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VOLUME IV NUMBER 2

# Lane Medical Lectures: The Lymphatic System

## Its Part in Regulating Composition and Volume of Tissue Fluid

By

CECIL K. DRINKER

Professor of Physiology and
Dean of the School of Public Health,
Harvard University

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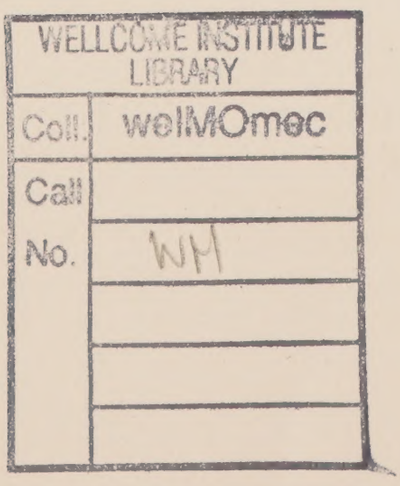

## THE LANE MEDICAL LECTURES

The Lane Medical Lectures were established in 1896 by Dr. Levi Cooper Lane of San Francisco, the founder of Cooper Medical College, which, in 1908, became the School of Medicine of the Leland Stanford Junior University. The University maintains the Lane Medical Lecture Fund, which is used to secure as lecturer at intervals of two years some eminent physician or scientist who has made a definite contribution in the field of medicine. The first series of lectures was given in 1896, and the total number, inclusive of the present series, is twenty-eight.

In 1927, action was taken by the School of Medicine to the effect that the formal lectures shall be published in a suitable journal, or in monograph or book form, according to arrangements to be made by the Committee on Supplementary Medical Education and the lecturer. Prior to this date, only the lectures for the years 1900, 1904, 1906, 1917, and 1924 had been published, and some of these only in part. Subsequent to 1927, all the lectures have been published in full, including a posthumous series, not actually delivered, by Dr. Rudolf Magnus. It is hoped that regular publication of the Lane Medical Lectures will be a means of extending their scientific value and influence.

The following courses of Lane Medical Lectures have been given:

1896. Sir William Macewen, M.D., Regius Professor of Surgery, University of Glasgow. "Surgery of the Brain."

1897. Christopher Heath, F.R.C.S., Eng., Professor of Clinical Surgery, University College, London. "Congenital Malformations, Aneurism, and Other Surgical Topics."

1898. Sir Thomas Clifford Allbutt, M.D., F.R.S., Regius Professor of Physic, University of Cambridge, England. "Diseases of the Heart."

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1900. Sir Michael Foster, K.C.B., D.C.L., Professor of Physiology, University of Cambridge, England. "History of Physiology."

1901. Sir Malcolm Morris, F.R.C.S., Edinburgh, M.R.C.S., Eng., Surgeon, Skin Department, St. Mary's Hospital, London. "Social Aspects of Dermatology."

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1906. JOHN C. MCVAIL, M.D., D.P.H., Cambridge, Glasgow. "Practical Hygiene, Epidemics, and Preventive Medicine."

1910. REGINALD HEBER FITZ, M.D., LL.D., Hersey Professor of Theory and Practice of Medicine, Harvard University, Boston, Massachusetts. "A Consideration of Some Features of the Lymphatic System."

1911. ERNEST FUCHS, Professor of Ophthalmology in the University of Vienna. "The Importance of Ophthalmology in Its Relation to Systemic Diseases."

1913. SIR EDWARD A. SCHAFER, LL.D., Sc.D., M.D., M.R.C.S., F.R.S., Professor of Physiology in the University of Edinburgh. "Internal Secretion."

1915. FRANK BILLINGS, M.S., M.D., Professor of Medicine in the Rush Medical College, Chicago, Illinois. "Focal Infection."

1917. SIMON FLEXNER, M.D., LL.D., Director of Laboratories, Rockefeller Institute for Medical Research, New York City. "Physical Basis and Present Status of Specific Serum and Drug Therapy."

1919. ALONZO ENGLEBERT TAYLOR, Professor of Physiological Chemistry, University of Pennsylvania, Philadelphia. "The Feeding of the Nations at War."

1921. L. EMMETT HOLT, M.D., Sc.D., LL.D., Emeritus Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, New York City. "Growth and Nutrition."

1924. LUDWIG ASCHOFF, M.D., Professor of Pathology, University of Freiburg, Germany. "Selected Topics in Pathology."

1925. VITTORIO PUTTI, M.D., Professor of Orthopedic Surgery, University of Bologna, Director Rizzoli Institute of Bologna, Italy. "Selected Topics in Orthopedic Surgery."

1928. F. D'HERELLE, M.D., Professor of Bacteriology, Yale University, New Haven, Connecticut. "Bacteriophagy."

1929. WALTHER STRAUB, M.D., Ph.D., Professor of Pharmacology, University of Munich, Munich, Germany. "Selected Topics in Pharmacology."

1930. CHARLES R. STOCKARD, M.D., Ph.D., Sc.D., Professor of Anatomy, Cornell University Medical College, New York City. "Constitution."

1933. J. C. DRUMMOND, Sc.D., Professor of Biochemistry, University College, University of London, London, England. "Biochemical Studies of Nutritional Problems."

1935. G. V. ANREP, M.D., D.Sc., F.R.S., Professor of Physiology, Egyptian University, Cairo, Egypt. "Studies in Cardiovascular Regulation."

1937. EUGENE F. DU BOIS, M.D., Professor of Medicine in the Cornell University Medical College, New York City. "The Mechanism of Heat Loss and Temperature Regulation."

1939. THOMAS M. RIVERS, M.D., Hospital of The Rockefeller Institute for Medical Research, New York City. "Viruses and Virus Diseases."

1941. CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology and Dean of the School of Public Health, Harvard University. "The Lymphatic System. Its Part in Regulating Composition and Volume of Tissue Fluid."

# AUTHOR'S PREFACE

The invitation to deliver the Lane Lectures found me reading proof of a book on the lymphatic system, and the idea of starting another book, even a small one, on the same subject seemed quite impossible. But these lectures are not easily given up. They have attained a place in American medicine which would have given great satisfaction to their distinguished founder. So I soon began to think about what I knew should not be done, and then to wonder whether in five short lectures it would be possible to describe a world never entered by the three-deckers we call medical texts, one of which I had just helped to perpetrate.

The end of it was a new sort of cruise in a ship built of experiments and ideas. Some of the timbers and planks are old and sound. The boring of time will ruin others. But that is no matter, since better workmen will replace them. I have tried my hand at developing the reasons why mammals have lymphatics; why the lymphatic system has been slowly turned from a casually organized accessory of the blood circulation into a physiological entity, complementing this first system and joining with it in the task of keeping the composition and volume of the mammalian tissue fluid at a steady normal level.

First of all, there is a brief account of the gradual evolution of the closed circulatory system of the blood—closed in the sense of having unbroken continuous walls—as against the primitive types of arrangement, which permit free and direct entrance of external fluids into the body. This is essentially a description of the way in which the environment of the body cells has been held constant, despite the extending character and the variability of the external environments encountered by higher animals.

This course sailed, it has been interesting to proceed historically for a while, and to show how the discovery of blood and lymph capillaries in vertebrates led slowly to a realization of the interdependence of the blood and lymph circulations, so vital for mammalian activity.

To illustrate this interdependence I have used recent experiments upon the relations of blood, lymph, and tissue fluid. The flow and composition of lymph from the heart were described a year ago. The same phenomena were seen experimentally in the lungs—certainly of great importance clinically—and described but a few months past. In neither case, can one as yet do more than indicate the steady physiological importance of the lymphatics, though there can be no doubt that these descriptions lead straight to medicine and surgery.

Finally, in spite of many difficulties, I have thought it possible—and here my ship may meet heavy going and dangerous rocks—to conclude with a description of the manner in which the blood and lymph circula-

tions take part in the healing of wounds and in the development of lung fibrosis following inhalation of dusts, choosing these common surgical and medical experiences to make my case, perhaps before it can be made.

To the technical skill of Dr. Madeleine F. Warren I owe the account of lymph flow from the lungs. Dr. Alfred C. Redfield has guarded me against the perils of invertebrate physiology as well as distance and difficult communication permitted. If these lectures, here and there, are proved wrong, it will be by experiment not by conjecture; and if, by a miracle, they are wholly right, then again they may incite inquiry. It has been my hope to leave you with exciting charts, which will be of no use until you explore the seas they picture and reach the harbors you desire. The voyages of medicine and surgery never end. One port gained, another lies just beyond the horizon; and lectures such as these, established forty-five years ago, are but guides to new and better ventures.

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HARVARD SCHOOL OF PUBLIC HEALTH
BOSTON, MASSACHUSETTS
October 1941

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# THE LYMPHATIC SYSTEM

# ITS PART IN REGULATING COMPOSITION AND VOLUME OF TISSUE FLUID

## I. PHYSIOLOGICAL PRINCIPLES DISPLAYED IN THE EVOLUTION OF THE MAMMALIAN CIRCULATION


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It is an interesting coincidence that thirty-one years ago Dr. Reginald Fitz delivered a series of Lane Lectures entitled "A Consideration of Some Features of the Lymphatic System." These lectures, the single preceding course from a member of the Harvard faculty, dealt with the problem upon which this lectureship has now asked a further accounting. It would have proved an interesting commentary on medical progress had it been possible to contrast the knowledge and beliefs expressed by Dr. Fitz with those which are current today. But, unhappily, neither from Reginald Fitz, Jr., nor from your library, can one find any trace of the 1910 lymphatic lectures beyond the small folder which announced them.

The time which has passed between these two lectureships has been filled with dramatic advances in the fundamental understanding of disease. Thirty-one years are a full measure of the productive life of a medical investigator, and the interval between Dr. Fitz and myself suffices for a generation of physiological and medical progress. The actual period has witnessed the pinnacle of achievement in the old classical physiology—a science in itself, and not, like the modern physiology, a general field where highly trained specialists, with little regard for the organism as a whole, play the tricks that go with limited interests and techniques. During the same exciting years, biochemistry has moved out of the hermitage of the

medical school laboratory and has entered every field of medicine and surgery where active progress is afoot. Following closely, physical chemistry has become one of the most useful tools for medical research.

The advance of knowledge concerning a subject such as the lymphatic system depends most often on two factors. The first of these is a realistic appraisal of the problems to be solved. By this, I mean the ability of the investigator to ask significant questions so that the answers will have real and not trivial consequence. In his foreword to the translation of Claude Bernard's *Introduction to the Study of Experimental Medicine,* Lawrence Henderson says of the great Frenchman:

"Thus it is possible to perceive his scientific method as the habit of the man. His life is spent in putting questions to nature. These questions are the measure of his originality. He cannot tell how they arise, but the experimental idea seems to him a presentiment of the nature of things. . . . .

"The experiment, accordingly, is always undertaken in view of a preconceived idea, but it matters not whether this idea is vague or clearly defined, for it is but the question, vague or otherwise, which he puts to nature. Now, when nature replies, he holds his peace, takes note of the answer, listens to the end and submits to the decision."[1]

It is not always mental quality or originality which causes the asking of profitable questions. Not infrequently they arise through the simple process of shifting a general method of attack which has proved brilliantly successful in an allied field to the one at hand. To illustrate: Between the years 1919 and about 1926, Krogh and his pupils showed that many of the functions of the blood capillaries could be learned by direct experiment, and need not depend upon uncontrolled deductions. My attempts—and, of more consequence, those of many associates—to attack the problems of the lymphatic system in the same direct way and often by the same methods, are a personal, though I believe a pertinent, instance of the influence which work upon one front may have toward instigating work upon another.

The second great factor making for new knowledge is found in the persistent development and use of new methods. In 1865, Claude Bernard said: "Medical investigation is the most complicated of all; it includes all the methods of anatomical, physiological, pathological and therapeutic research, and as it develops it borrows a host of research methods which become powerful allies. All progress in the experimental sciences is measured by the development of new techniques for investigation. The entire

[1] From L. J. Henderson's introduction to Claude Bernard's *An Introduction to the Study of Experimental Medicine,* translated by Henry Copley Greene, p. vi. The Macmillan Company, New York, 1927. Quoted by permission of the publisher.

future of experimental medicine depends upon devising a method of research which may be applied profitably to studies of vital phenomena in normal or in pathological conditions."[2]

In the observations upon the lymphatic system which I shall describe, two techniques were indispensable. The first was the rapid development of microchemical methods, which permitted extensive and repeated analyses of blood and lymph without unfortunate depletion of the animal. For example, among the many spectacular achievements from Ludwig's laboratory in the eighties of the last century was the cannulation of small subcutaneous lymphatic vessels in the legs of dogs—a remarkable instance of manual dexterity, considering the anesthesia available. But such an operative accomplishment, though providing ample material for the biochemist of today, at the time led to little, the amount of lymph collected being so small as to defy the current methods of chemical examination. This biochemical inadequacy existed even after the lectures of Dr. Fitz in 1910, since the modern era of micromethods in medical research began about 1920.

The second technical advance was the increasing ease with which it has become possible to isolate and cannulate even the smallest blood and lymph vessels. Two methods are used in such experiments, and both have been employed in the investigations upon the lymphatics. There is, first, the method of minute dissection, carried out usually under 2- to 6-power magnification and requiring various types of binocular magnifiers. In such dissections and cannulations of vessels, special forceps, scissors, etc., are used, but all instruments are held in the hands of the operator and not in clamps manipulated mechanically. When the "tricks of the trade" are learned—and it does not take long, provided one has the right sort of instruments—vessels down to half the diameter of a common pin may be isolated, cannulae introduced, fluids collected, pressures measured—in short, all the procedures may be carried out which have been used so constantly and so long in studies upon the grosser parts of the blood circulation.

This first technique, essentially dependent upon good eyes, good hands, and instruments correctly designed and, above all, correctly sharpened, is not new; and even in the most adroit operator I doubt if skill has appeared comparable to that shown by the eighteenth-century biologists—as, for example, by the Dutch dissector Lyonnet and later by Straus-Durckheim, who published a monograph on the minute anatomy of one of the common beetles of Europe. Fortunately, in a later book on comparative anatomy, Straus-Durckheim (1843) included drawings of his instruments, which has permitted the resurrection of some of them and their use today. For

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[2] From Claude Bernard's *Introduction à l'étude de la médecine expérimentale*, p. 26. J. B. Baillière et fils, Paris, 1865.

illustration, Figure 1 shows the adjustable scissors devised by Straus-Durckheim, together with similar scissors made from this drawing under the direction of Professor Krogh. These scissors prove very capable aids when one is working upon structures so small as to be about at the limit of freehand manipulation—structures requiring section without motion beyond that of a minute and strictly limited cut of the scissors. Straus-Durckheim writes of his fine cutters as follows: "The difficulty experienced

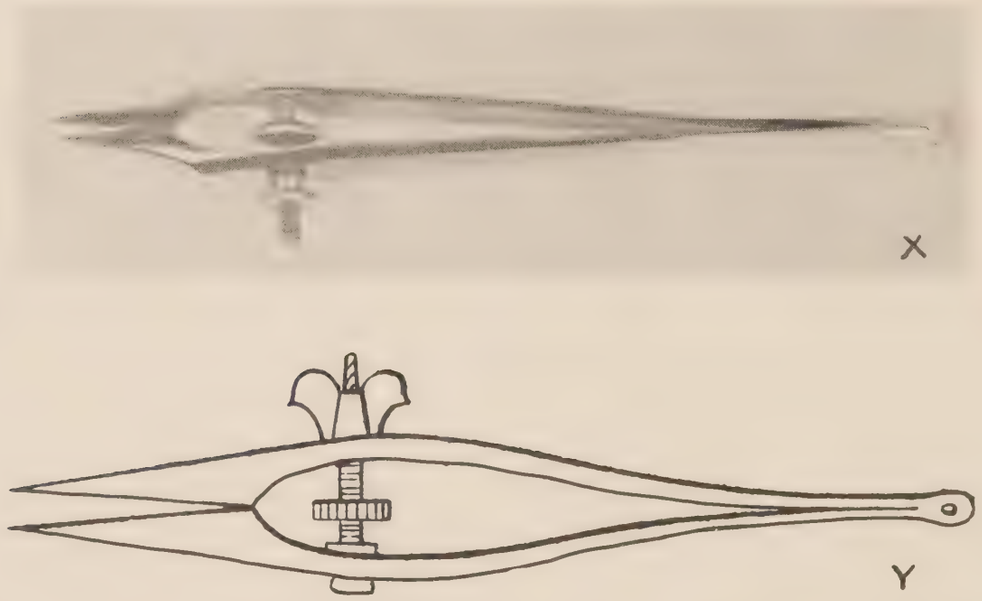


FIG. 1.—Lower illustration, *Y*, the scissors called "microtome" by Straus-Durckheim (From Straus-Durckheim, Vol. 2, Plate 4, Fig. 59. See footnote 3, below.) Upper illustration, *X*, a copy of the "microtome" made under the direction of Professor Krogh from Straus-Durckheim's illustration.

with precise cutting of very small objects by means of ordinary scissors caused me to try to devise another instrument to replace and improve them and this I have described under the name of microtome and have found it most efficient."[3] Much later, and under protest from certain of the anatomists, this designation was conferred upon the machines for section cutting which in so many forms are used today.

The second technique, and that required for work upon the finest blood vessels and lymphatics, utilizes micromanipulation of pipettes and instruments under magnifications which have become higher and higher as new experimental requirements are met. This does not mean lack of similar attempts and, indeed, of great contributions by the early biologists, but merely that without the microscopes and means of illumination available

[3] From H. Straus-Durckheim's *Traité pratique et théorique d'anatomie comparative*, Vol. 1, p. 152. 2d ed. Mequignon-Marvis fils, Paris, 1843.

today progress was necessarily limited. The difficulties, indeed, the mysteries, of such work are not so real as they seem, provided correct instruments, lighting, etc., are available. With makeshift equipment, the most philosophic investigator soon goes mad!

Let us turn now from introduction and from this brief note upon methods to explore some of the actualities of the blood and lymph circulations—two separate systems, yet so perfectly integrated as to preclude separate discussion.

Consider, first, a typical blood capillary in a mammal—perhaps an anomalous conception, since in a later lecture the structural differences of capillaries in many parts of the body will be noted. It is an endothelial tube, about 8μ in diameter but displaying very considerable variability in caliber, though always thin-walled. At first the capillaries were thought to be permeable to water and to the simple solutes in the blood, but not to the blood proteins. This last conviction has had a lingering death. Starling (1895–1896) showed that the blood proteins possess a slight osmotic pressure, and that lymph containing protein is essentially a filtrate from the blood capillaries, perhaps modified in the tissues and in the lymphatic capillaries. Even in his day, it was believed that the salt content of blood and tissue fluid was identical. In addition to water and salts, one had dissolved proteins in the blood capillaries, which added an osmotic factor of low but fairly constant value—called by Starling the colloid osmotic pressure —and important for absorption of water by blood. Operating against this influence for absorption Starling placed the capillary blood pressure, which, under ordinary circumstances, tended to force water out of the capillaries so as to balance the osmotic attraction of water into these vessels. As conceived by Starling, the situation is shown in Figure 2.

The essentials of Starling's conception have not been seriously traumatized by modern biochemists and physical chemists, in spite of better technique and much effort. The main fact which has become clear is that the typical blood capillary is not impermeable to the blood proteins, in the strict sense which was maintained during the early flowering of biochemistry, but leaks a small amount of these compounds even at normal capillary pressures. This realization has no real effect on Starling's conception. It merely causes us to reduce the figure for the effective colloid osmotic pressure of the blood plasma, since blood proteins outside the capillaries have the same influence upon possible water movement as those within and must therefore reduce the potency of the blood proteins for absorption of water into the circulation.

In summary, the wall of the blood capillary is completely permeable to water and blood solutes until molecules of the size of serum albumin are reached, when, although passage of the capillary membrane is possible,

capillary pressures equaling the effective osmotic pressure of the plasma proteins are necessary to force such molecules through in any considerable amount. Water and compounds of lower molecular size than serum albumin diffuse freely through the capillary endothelium, but when molecules of the size of serum albumin are involved a definite capillary pressure or

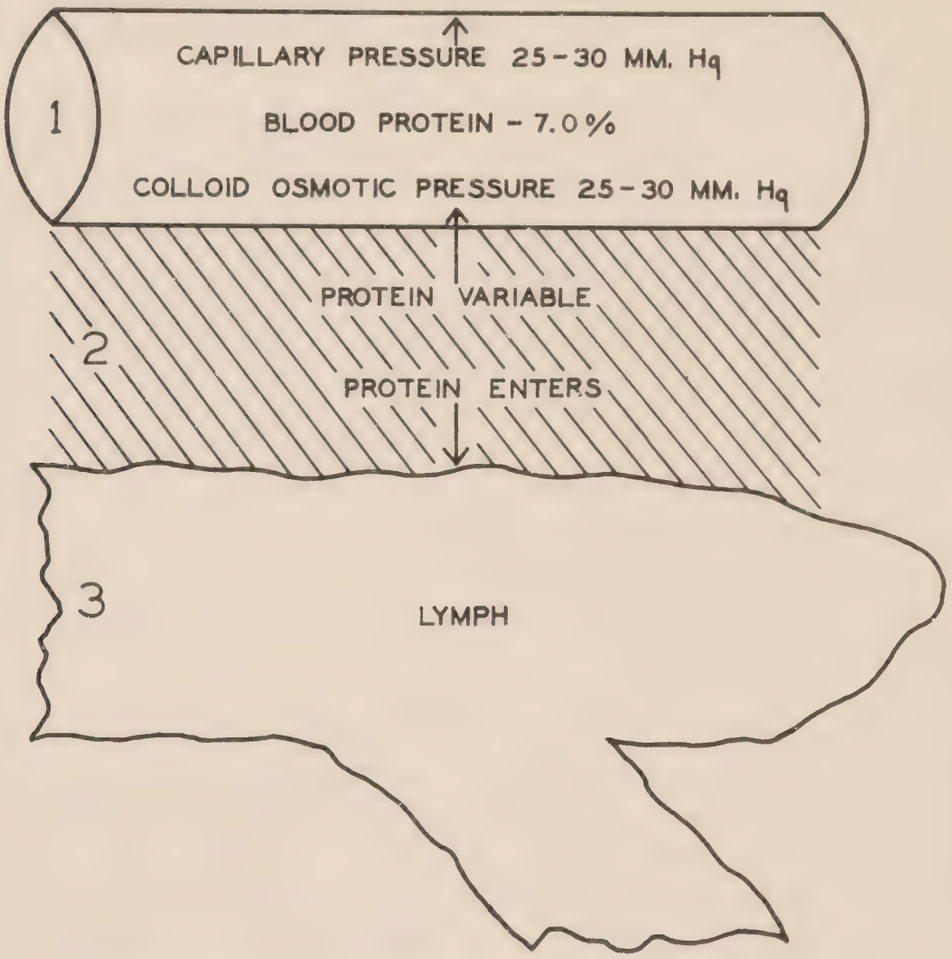


FIG. 2.—Diagram to show the relations of capillary blood, tissue fluid, and lymph in mammals: *1*, blood capillary; *2*, tissues bathed in fluid, *3*, lymph capillary.

alteration in the capillary endothelium is necessary in order to result in their escape from the vessels. In final analysis, this means that the greatest normal variables in the tissue fluid, the true environment of the body cells, are the blood proteins.

Until the appearance of an important series of researches in 1940, it has always been a puzzle to me as to how quiescent, bedridden patients avoided the gradual development of, at least localized, slight edema. It was my belief that the normal proteins of the tissue fluid (serum albumin, serum globulin, and traces of fibrinogen) had but two destinies, since there was no good evidence of their direct re-entrance into the blood capil-

laries except in traces. The first of these depended upon lymphatic function. If movement of the part or other influence forced the tissue fluid proteins into lymph capillaries, they were returned to the blood by the lymphatic route.

But what might be expected to result if the lymphatics were blocked or entire immobility caused no flow of lymph? Under such conditions, the first and easiest fate of extravascular proteins is not possible, and a second destiny must await them. It is reasonably certain that there is a constant, though extremely slight, leakage of protein from blood capillaries in a part at rest, provided the circulation is normal; nor does lymphatic blockage stop this escape of protein. At the same time, reabsorption of water by the blood capillaries slowly diminishes, since mounting extravascular protein concentration holds water and counters the colloid osmotic pressure of the proteins in the blood. The logical result should be the development of edema, due to accumulation of proteins in the tissue fluid. The facts, however, are that an immobilized leg, where there is no reason for increased capillary blood pressure, does not become edematous. Edema may be caused by lymphatic blockage, even in the absence of inflammation; but even this edema fluid is not characterized by steady increase in the concentration of protein to the level of that in the blood plasma. Something beyond the conventional beliefs as to the fate of tissue fluid proteins derived from the blood must certainly occur.

This predicament did not disappear until it was shown, through the work of Whipple and his associates (see Madden and Whipple, 1940), that if dogs were given dog plasma intravenously they could be kept in nitrogen equilibrium and needed no other source of protein. There could be no conclusion save that extravascular serum albumin and serum globulin were digested and utilized by the cells in the part. It was then realized that in a splinted leg, where capillary blood pressure is low and lymph movement negligible or absent, undue accumulation of blood proteins in the tissue fluid was prevented by their utilization *in situ*. The practical implications of these findings, and they are many, will be discussed in the final lecture.

In contrast to the simple condition of a bedridden invalid, in the main lying relatively motionless, in whom loss of proteins from the blood capillaries into the tissues is slight, consider the state of affairs in a runner, particularly as he approaches exhaustion and his venous pressure begins to rise, with attendant slower flow through the capillaries, increased capillary pressure, and perhaps some anoxemia. Under these circumstances, escape of proteins from the blood into the tissues will increase. It will occur rapidly, and some degree of swelling of the legs is frequent after an exhausting run. It would be even greater, were it not that the motions

of running force extravascular proteinized fluid into lymphatics and along lymphatics back to the blood, thus restraining excessive accumulation of the tissue fluid. It thus becomes evident that normally the lymphatic system in mammals is an emergency spillway for oversupply of blood proteins to the tissue fluid. The lymphatics, lacking independent propulsive organs, such as the lymph hearts so prominent in amphibia, are dependent upon some external force to return the lymph to the blood. Lacking such influences, the blood proteins will remain in the tissue fluid unless they are broken down and utilized by the body cells, or as smaller molecules, the products of local digestion, enter the blood capillaries and disappear promptly.

On the basis of these principles, presented diagrammatically in Figure 2 and illustrated by familiar experiences, the essential features of the relations of blood and lymph in the mammal may now be listed. They are:

1. A closed system of blood capillaries with endothelial walls of varied permeability but capable of retaining practically all of the blood plasma during the usual conditions of rapid capillary transit.

2. A variable hydrostatic pressure in the capillaries.

3. A mixture of extracellular nonrespiratory proteins in the blood to which the capillary endothelium is somewhat permeable.

4. An extravascular tissue fluid, lower than the blood plasma in content of blood proteins but in other respects practically identical with plasma.

5. A system of closed lymphatic capillaries with extremely permeable endothelial walls, which lacks any inherent propulsive mechanism to move lymph into larger valved vessels but is dependent upon inconstant and extraneous forces, such as those of muscular activity or massage, to cause entrance of fluid, cells, and particles into lymphatic capillaries and eventual flow of lymph back to the blood.

It is impossible to trace these five physiological characteristics from primitive animals to mammals through the conventional systematic relationships which depend upon structural similarities. Our interest is in the evolution of a complicated group of processes; and, as will be seen, the existence in lower animals of a few or most of the elements in the physiologically co-ordinated system found in mammals is not related to similarities in general structure but depends far more upon the life the animal must lead.

Turn, first, to a very simple functional arrangement of cells and body fluid, such as is found in a sponge or jellyfish. There is a body cavity, enclosed by two layers of cells and freely entered by sea water, upon which such creatures depend for oxygen and food. A few floating cells but no dissolved protein are found in the coelomic fluid. There is no

separation of the external environment, sea water, from the internal environment of the body cells. Figure 3 is a diagram showing the extreme

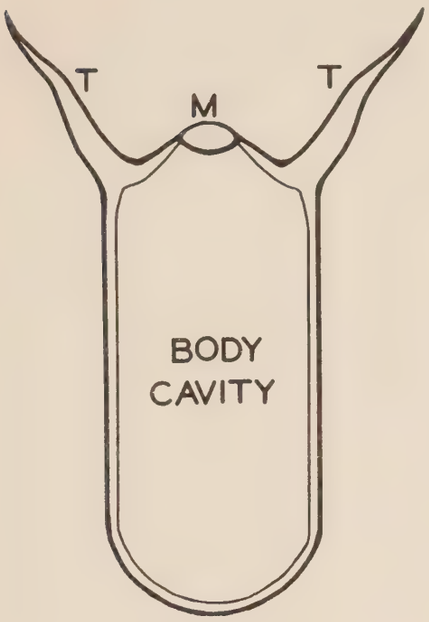


FIG. 3.—Diagram illustrating the simple relation of cells to body fluid in a sea anemone, a coelenterate. Sea water enters an opening, *M*. The body cavity is enclosed by two layers of cells. *T*, tentacles.

simplicity of such organisms, which do not display even a suggestion of a vascular system or of the other factors found in mammals.

So far as body fluid is concerned, the common starfish is not far different. Again there is a body cavity which is filled with sea water but which—perhaps as a vague expression of increasing complexity and the beginning isolation of the internal environment of the animal from its external environment of sea water—contains fairly numerous cells and traces of protein. This coelomic fluid does not clot, and the nature and significance of the protein is not known. But even amongst the echinoderms—of which phylum the starfish is a member—animals are found displaying progress toward the goal we are seeking. Thus, *Cucumaria,* a sea cucumber, one of a number of sausage-shaped creatures belonging to a different class from the starfish, has a large body cavity and, in addition, an abbreviated but distinct set of blood vessels with branches ramifying through the mesentery and around the gut. Figure 4 is a diagram of this rudimentary arrangement. In *Cucumaria,* the body fluid contains traces of dissolved protein and many nucleated cells filled with hemoglobin. The vessels contain fluid, which is said to differ in the content of dissolved protein from that in the coelom and contains variable numbers of erythrocytes. At best, the animal has but a rudimentary vascular system, in all parts of which the pressure is negligible and the extracellular protein so low as to be equally without influence upon water exchange. The whole

arrangement, though seeming crudely to forecast future developments, in reality is simply a way of meeting the needs of the enviably quiet life enjoyed, I trust, by *Cucumaria.* The sea cucumber is a fisherman, orderly, quiet, and wholly devoted to the seizure and consumption of such creatures as swim within reach. It must meet but limited requirements for growth, and, finally, is spared the excitements of sex through an apparently competent hermaphroditism which produces ample numbers of new cucumbers.

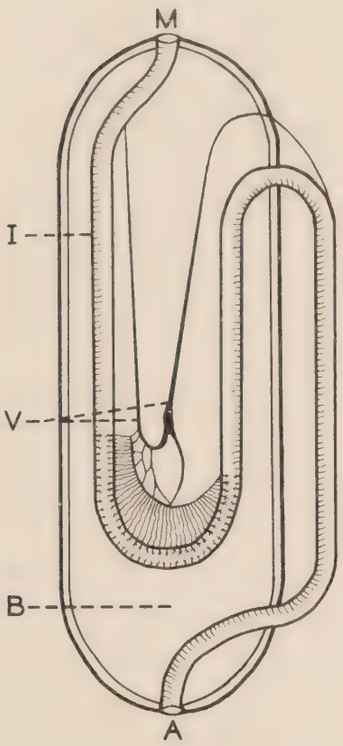


FIG. 4.—Diagram of a vertical section of a sea cucumber, an echinoderm. *M,* mouth; *I,* intestine; *V,* blood vessels, shown ramifying through the mesentery and intestinal wall in part of a loop of intestine; *B,* body cavity; *A,* anus.

The blood of a large number of invertebrates contains the copper-containing respiratory protein, hemocyanin (Redfield, 1933; 1934), which is invariably dissolved in the blood and is the sole blood protein. Such animals have vascular systems of different degrees of complexity, which contain blood at pressures measured so far only in the large vessels.

Figure 5 is a diagram of the circulatory system in a lobster. The pressure in the posterior aorta of this animal averages 14.25 cm. of water, or about 10 mm. of mercury. This must mean a very low pressure in the sinusoidal spaces which surround the principal organs. From them the blood passes through the venous sinus into the pericardium and enters the heart. The arterial blood is said to reach the tissues directly, moving slowly at low pressure through tissue spaces unlined by an endothelial membrane, so that the mechanism for exchange of water and solutes between blood and body cells gives little evidence of organization upon the

mammalian pattern, and lacks also any provision for emergency delivery of oxygen—that is, any arrangement to provide for sudden bursts of activity such as are so characteristic of many mammals.

The lobster depends upon the beating of its heart to force blood out to the tissues, where blood flow is dependent upon extraneous forces such as muscular contraction. The condition is very similar to that presented by lymph movement in mammals. In them water and a certain amount of blood protein leave the capillaries, and eventually a part of this fluid

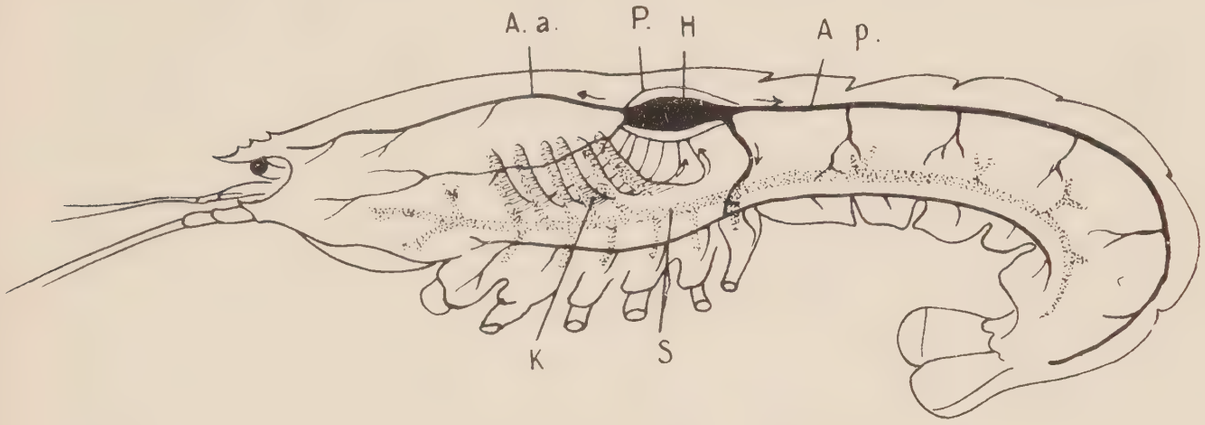


FIG. 5.—A schematic view of the circulatory system in a lobster. *H*, heart; *P*, pericardium; *Aa* and *Ap*, aortae giving off small branches; *S*, venous sinus; *K*, gills. (From *Handbuch der vergleichenden Physiologie*, Vol. 1, p. 680. Edited by H. Winterstein, Jena, 1925.)

enters lymph capillaries, to move on through the lymphatic system. Once out of the blood capillaries, no force inherent in the lymphatics sends the lymph back to the blood. Contraction of muscles, massage—some outside influence—accomplishes this.

With the lobster, contrast another invertebrate, the squid, which also depends upon hemocyanin in solution to transport and deliver oxygen to the tissues. The adult squid is a free-swimming mollusk, capable of astonishing activity and not restricted to the slow, tenacious use of muscle seen in most of his molluscan relatives. He is capable of pursuing and devouring herring, and has been said to leap twelve feet out of the sea. Recently, Duncan (1941) has described the fighting qualities of the giant squid when taken on rod and reel—an account of physical power seductive to the fisherman, and to the physiologist an intriguing picture of functional efficiency.

How is the squid able to accomplish this sudden and violent activity? First, amongst the bloods containing hemocyanin, that of the squid and his near relatives has the greatest capacity to carry oxygen; and the physicochemical situation of squid hemocyanin makes for quick delivery

of oxygen to the tissues. Second, the squid has a circulation which is not only closed, but displays very definite meshworks of capillaries lined by a single layer of endothelium. Williams (1902) made injections of the circulation in the squid and silver impregnations of the capillaries. In nearly all parts of the body, he demonstrated capillary nets similar to those in the mammal. Here, then, is an animal with a capillary circulation on the mammalian pattern, a circulation presenting a large surface for exchange between blood and tissues and capable of supplying oxygen and blood solutes efficiently and, if necessary, very rapidly. The pressure of the blood in one of the aortae of the octopus (an allied form) varies between 25 and 80 mm. of mercury. What the pressure in the capillaries of the squid may be is not known, but that the capillary walls must often withstand a substantial strain, tending to force water and solutes out to the tissues, is apparently certain. Though the squid possesses a capillary circulation resembling that of the mammal, his blood contains no extracellular proteins, such as serum albumin and serum globulin, which exert a low but definite osmotic pressure capable of causing absorption of water, provided opposing forces are not too great. Is it possible that the dissolved hemocyanin not only carries oxygen but also exerts an influence on water movement similar to that of the extracellular blood proteins in mammals? Perhaps so; but, lacking measurements of capillary pressure and the osmotic pressure of squid hemocyanin, one cannot conclude that in this common mollusk one encounters a condition so fundamentally important in higher forms.

A final interesting fact relative to the capillaries in the squid is their impermeability to hemocyanin, which is thus preserved for respiration. But if hemocyanin is injected intravenously into a frog or a mammal, it passes out of the capillaries very promptly and is easily detected in the lymph. One cannot be entirely sure that this escape is not due to poisoning of the walls of the frog capillaries by hemocyanin; but it is of equal interest that in all animals where the respiratory pigment is intracellular hemoglobin, if dissolved hemoglobin is given intravenously, the compound passes through the capillary walls at once and is lost as a carrier of oxygen. At the same time, there are many worms in which dissolved hemoglobin is the respiratory pigment; and in such creatures it is not lost through the walls of the blood vessels, as is the case when free hemoglobin circulates through the capillaries of animals in which the pigment is normally intracellular.

It is thus clear that even a brief review of lower forms shows an entire lack of systematic progress toward the establishment of the methods of exchange between blood and tissues found in mammals. One habit of life of certain lower forms—existence characterized by fairly constant ac-

tivity, with spurts of intense physical effort—occasionally brings indications that the principles existing in mammals are operative to a certain degree in primitive animals of fair body size. The squid is a case in point. Many insects too are capable of astonishing degrees of activity; but in them small size, let alone other factors, makes possible the supply of oxygen and nutrient materials which are essential for their mode of life. Other influences than physical activity are served by the circulatory arrangements found in mammals; but so far as invertebrates are concerned this factor, activity, coupled with reasonable size, comes nearest to correlation with the functional organization of the higher animals.

When vertebrates are reached, one at once encounters, not tendencies toward, but examples of the five features listed as governing the relations of blood and lymph in mammals. Let us consider, from the point of view of these five features, what is found in the most primitive creatures which still make up the largest part of vertebrate life upon our planet, fish.

1. The vascular system of fish possesses capillaries with continuous walls, which are in the main similar to those in the mammal. Indeed, one of the first reasonably satisfactory descriptions of the capillary circulation deals with vessels in the fins of fish. Many of the older descriptions speak of spaces unlined by endothelium, but as technique has improved the integrity of the capillary walls has been firmly established (von Skramlik, 1935). There is a fairly efficient heart, and the blood returns to it through valved veins.

2. There are many measurements of pressure in the largest arteries, and the figures vary greatly even for the same species. Greene (1904) found values as high as 120 mm. of mercury in the ventral aorta of the salmon, so that there must be a considerable capillary pressure, though, so far as I know, it has not been measured for the salmon or for any other fish. In contrast to the high blood pressure of the salmon, a fish whose magnificent activity is happily familiar to many Californians, Turner and Haywood (1937) reported the pressure in a large abdominal artery of a number of fish collected in Norway and at Woods Hole. There were eight different elasmobranchs, dogfish, sharks, skates, and the like, and five teleosts, sea bass, cod, pollack, etc. Pressures were recorded in centimeters of physiological saline, and the highest was 37 cm. for the common sea bass of the East. This means 27 mm. of mercury. The same artery of the dogfish gave 12.3 mm. of mercury. And so it went. These sluggish fish, all giving low pressures, are voracious feeders, which do the least possible work for what they obtain. Judging from their blood pressures, they are incapable of such bursts of activity as characterize the salmon and the different mackerels.

3. Fish blood, like that of all vertebrates, consists of plasma containing

dissolved proteins and cells carrying the respiratory pigment, hemoglobin. Redfield pointed out in 1933 that even the few measurements of protein concentration then available indicated that as the activity of the fish increased, blood protein concentration increased. His reasoning was obvious. With activity goes augmented capillary pressure, and lacking a higher protein content of plasma to give a balancing colloid osmotic pressure, the fish would surely lose undue amounts of water from his blood whenever pressed to great exertion by the need to obtain food or to avoid being food.

The colloid osmotic pressure of blood is due to serum albumin and serum globulin, somewhat more to the former because of its smaller molecule. In man, the ratio of albumin to globulin is about 1/6, and the total protein in the neighborhood of 7.0 per cent. The result is a colloid osmotic pressure of 25 to 30 mm. of mercury. These figures for man, qualified as they are, emphasize a degree of variability for which there are many causes. One of the simplest is a lower *A/G* ratio; that is, assuming a total protein of 7.0 per cent, there is an undue proportion of globulin, and a lower colloid osmotic pressure will result. Figures such as these have been obtained many times, more often for man than for other vertebrates; and if there is variability in the figures for normal men, who are fairly uniform in physical characteristics and habits, it is not surprising that in fish, which differ so markedly and in so many ways, much greater variability is found. Actual figures for fish are woefully few. Turner (1937) found that the blood of the common bonito, *Sarda sarda,* had a colloid osmotic pressure of 17.1 mm. of mercury. The same measurement, averaged for bloods taken from ten toadfish, *Opsanus tau,* was 7.7 mm. of mercury. The bonito, one of the mackerels, is a pelagic fish, always in motion and feeding largely upon creatures of nearly equal speed and agility. Many other things, such as a large gill surface and, I believe, a large blood volume, have their part in enabling the bonito to accomplish his strenuous existence. In this active fish the capillary blood pressure is probably comparatively high, and to balance this the concentration of blood protein and the proportion of serum albumin must be great enough to produce the high colloid osmotic pressure of 17.1 mm. of mercury.

The toadfish, on the other hand, is a solitary and disagreeable sort of gangster, who hides in an old tin can or a discarded rubber boot, and lives with little exertion and malign satisfaction upon the unfortunates who come within easy reach. His colloid osmotic pressure is low, and his total blood protein slightly over 1 per cent. Perhaps his capillary pressure rises somewhat if a particularly desirable crab begins to enter his hide-out, but a long and unfriendly acquaintance with *Opsanus tau* does not cause me to rate his emotional organization very highly. He arouses violence and

profanity in many a follower of the gentlest art, angling; but if he could speak it would be as Dickens's Fat Boy, "I likes eating!" and this end is attained by ambush. Here, then, is a fish physically sluggish and obviously so ordered by nature. Did he attempt the career of the bonito, he would be as out of place as the East Coast crews so often are when they measure their power against the West Coast eights! I am inclined to believe that of all the innumerable qualities which characterize vertebrates, activity—sudden and fairly prolonged muscular exertion—comes nearest to correlation with the fundamental properties of the circulation.

Fish, however, are less fixed in their plasma protein concentration than are mammals. Turner (1940) studied the protein content and colloid osmotic pressure of another series of fish, in which she observed the effects of plasma protein changes as a result of diet and bleeding. The results indicated that lack of protein in the food affected the concentration of plasma protein very quickly, so that in the natural state fish apparently experience a rise and fall of blood protein, dependent upon their success in obtaining food, which is far more rapid than is the case in their distant vertebrate relatives, the mammals. For example, *Centropristes striatus,* the common sea bass, when freshly caught had a blood protein of 2.9 per cent and a colloid osmotic pressure of 7.2 mm. of mercury. With a few days of plentiful food, the same fish attained a blood protein concentration of 5.4 per cent and a colloid osmotic pressure of 15.4 mm. of mercury.

Upon bleeding, if food was adequate, protein regeneration was very rapid, and all the indications were thus toward a variable rather than the relatively stable blood protein concentration found in mammals. Unfortunately no albumin and globulin determinations were made, but the rapid changes in plasma protein caused the belief that fish depend markedly on plasma proteins for nutrition, and depend less than do mammals on these substances for maintaining water balance between blood and tissue fluid.

All of this discussion is not to illustrate the physiology of fish, but to point out the fact that methods which are being applied constantly to the blood of mammals would yield very significant information if applied to these lower vertebrates. It is of little profit to make a single measurement—such as the concentration of protein—in fish blood. What are needed are data, from the same fish, on the five features emphasized as fundamental in the mammalian circulatory apparatus, data such as may now be secured from a single dog. Such information, correlated with other data, would do much toward telling the human variety of mammal why he is as he is.

4. The fourth of the five features of mammalian circulatory exchanges is "an extravascular tissue fluid, lower than the blood plasma in content of blood proteins, but in other respects practically identical with plasma."

The composition of the tissue fluid, the real environment of the body cells, has been one of the great problems in medicine and physiology since Claude Bernard, in 1865, so clearly defined the medium in which the organism really lives. It is worth while to recall another paragraph from his *Introduction to the Study of Experimental Medicine,* realizing that for his clear mind experimental medicine and physiology were one subject:

"In all living creatures, the internal environment, which is a true product of the organism, preserves the necessary relations of exchange and equilibrium with the external cosmic environment. But in the degree the organism becomes more complex, the internal environment becomes more specialized and more isolated from the external environment. In plants and in cold-blooded animals this isolation is less complete than in warm-blooded animals. In the latter the blood possesses a temperature and composition which are very nearly constant. . . . . The vital manifestations of animals vary only because the physico-chemical conditions of their internal environment vary."[4]

Bernard included all the body fluids in his conception of the internal environment, and considered the circulating blood as the dominant factor in maintaining the constancy of the tissue fluid. In normal vertebrates the amount of tissue fluid—that is, free fluid containing solutes including the blood proteins—is undoubtedly slight, and collection of such fluid uncontaminated by blood has been accomplished from frog muscle alone (Maurer, 1938). The composition of the fluid has therefore been largely a matter of deduction from studies of the blood, of edema fluids, and more recently from analyses of blood and lymph collected simultaneously from the same tissue area.

5. The final feature of the mammalian circulatory system is the lymphatic apparatus, vessels and nodes. Lymphatics are found first in fish. This means a system of endothelial-lined vessels in no way connected with the arteries, but communicating with the veins. The number of venous entrances varies, being large in many selachians (sharks, dogfish, etc.) and coming down to two in most teleosts (perch, cod, salmon, etc.). Lymph nodes are not found in fish, though accumulations of lymphocytes occur; and the lymphatics do not possess valves, so that if pressure rises in the veins blood is readily forced into them. There can be no doubt that in fish, as in mammals, the lymph capillaries collect fluid and solutes, particularly those of large molecular size, such as serum globulin.

In most fish the movement of lymph toward the veins is apparently dependent upon bodily activity, and must be a very casual process. The common eel, the conger, and the lamprey possess a lymph heart near the

[4] From Claude Bernard, p. 110. See footnote 2, p. 13.

tail, which forces lymph into a vein (Fig. 6). Such hearts are very important in the amphibia, where the lymphatic circulation is an extremely active part of the general circulation.

The sudden appearance in fish of a new and elaborate set of vessels, the lymphatics, is an extraordinary phenomenon. Why should this happen? There are a number of possible reasons, but none is satisfactory. Little is known of the blood proteins in fish. Lepkovsky (1929–1930) found great

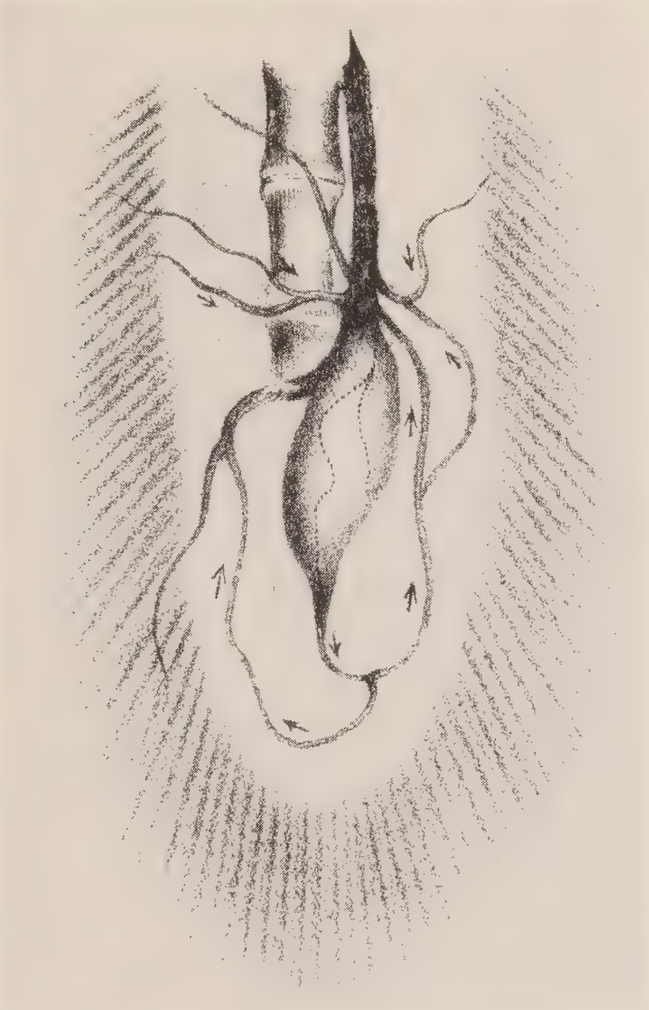

FIG. 6.—The caudal heart of the eel, the first illustration of a lymph heart, described as "a palish sack." Marshall Hall believed this heart a part of the blood circulation since he often saw red corpuscles in it. These were due to regurgitation from the vein. The lymph heart possesses valves, but the lymphatics of fish lack them, so that back flow in the vessels occurs readily. (From Hall, 1835, Plate X, opposite p. 168.)

variation in the $A/G$ ratio in a few species. The colloid osmotic pressure will be related to such differences in composition, and so will the capillary blood pressure. I need not list all the facts which could be gathered in the

course of investigations upon this general problem. For me, one of the most important items is the permeability of the capillary endothelium. Is it like that of the frog, which permits constant and rather free escape of blood proteins? If so, the protein must be used as an important source of tissue nutrition or be returned to the blood by a special route, the lymphatic vessels. Furthermore, regardless of visible structure, the permeability of the blood capillaries is not fixed in any animal. It varies with common conditions, such as oxygen lack, prolonged distention of the capillaries, and many other influences. But given a normal fish—and a large one will be needed—arranged so that lymph as well as blood can be collected, it should be possible to make at least a crude set of observations upon the permeability of the capillary endothelium by intravenous injection of a variety of substances and by other methods.

The secret of endothelial permeability may reside in the nature of the capillary wall, or permeability may be brought about in other ways. In mammals it is apparently necessary that molecules of the size of serum globulin reach the tissue fluid, even though sparingly. For example, when intravenous injections of antisera are used in efforts to check generalized infections, it has been shown that though the blood capillaries permit escape of antibodies, the lymph contains these in proportion to the protein content, and so never in the concentration found in the blood. This fact and other evidence indicate the normal degree of capillary permeability, and give an idea of the size limits of molecules reaching the tissue fluid from the blood under ordinary conditions.

The idea that the lymphatic apparatus—cells, nodes, and vessels—is essentially a defense mechanism is an old one and in the main has been concerned with the lymphocytes and lymph nodes; but if the antibodies distributed by the blood are proteins of the size of globulins, it would seem that a certain degree of capillary permeability to proteins is an important factor in the reactions of immunity. Yet with substances in the nature of globulins capable of leaking through the capillary wall, the normal blood proteins also will escape; and, lacking a lymphatic route back to the blood, they must either be used *in situ* or must accumulate and cause edema.

Out of this confusion of suggestion and possibility, one fact is surely clear. We do not know many of the reasons why the lymphatic system has appeared, and we know but a fraction of what it does. We know that it gathers complexity upon complexity from fish to man, and that in man and mammals disastrous experiences follow ablation of function, either of vessels or of lymphoid tissue. We know that the lymphatics carry substances away from the tissues which could not be disposed of otherwise and which must not be allowed to accumulate locally. But it is hard to consider such disasters or such performances from the point of view of evolution.

One can appreciate the gradual, if irregular, attainment of intracellular hemoglobin and other factors making for successful respiratory exchange in mammals. In contrast, the lymphatic vessels, set aside as a system separate from the arteries and capillaries and emptying into the veins, give no evidence of even a broken and irregular evolution. In fish, one suddenly finds a very important element of the physiological organization of mammals. Why has this happened and what is the real meaning of the lymphatic system?

The answer lies in experiment. Theories are not answers; they are merely incitements to experiment in order to answer questions. I have no objection to theories, but they are the cocktails not the roast beef of science. In experimenting it would seem wise to examine the lymphatic system and its functions in fish, rather than, as my associates and I have done, to struggle with the vastly more elaborate system of mammals. If this course were taken, since the lymphatic circulation can never be considered physiologically without concomitant appraisal of the blood circulation, I venture to believe differences in the relations between the five essential features making for exchange between blood and tissues would be found, and it would be possible to correlate these variations with the physiological requirements of the organism. Based on such evidence, the reasons for the appearance and elaboration of the lymphatic circulation would, perhaps, become clearer.

Between fish, which present the most primitive expression of the five essential circulatory features, and mammals, which have them in highest complexity, there lie amphibia, reptiles, and birds. If we hunt our circulatory quarry through these different classes of vertebrates, no new principles are uncovered. One finds, particularly upon the side of the lymphatics, what seems to be a straightforward increase in complexity; and this in turn must rest upon greater and greater need for the lymphatic system. Why should this be? Why do mammals—and in man the development and relations of the blood and lymph systems reach final complexity—require such a formidable circulatory equipment? Lymphatics appear first in fish. They are without valves and there are no lymph nodes. Amphibians—at least the frog—have a circulation of lymph so rapid and extensive as to function as part of the blood circulation, not as a system containing fluid, etc., which may remain in it for some time, but as a system arranged for the rapid and regular delivery of substantial quantities of proteinized fluid back to the blood. In reptiles the lymph circulation is less rapid, but the vessels are very numerous. In certain birds lymph nodes appear, and curiously enough these filtering elements are at the base of the neck in the line of the cervical lymph streams to the thoracic and right lymphatic ducts. They are not in the line of drainage from the intestine.

Finally, mammals—and most of all man—display blood and lymph circulations in the greatest elaboration. Undoubtedly a number of factors essential for maintaining the constancy of the internal environment are responsible for this. No one can list all the reasons for the complicated arrangements with which man finds himself endowed; the more so since his physiological reactions not only meet the needs of healthy, normal life, but also—and with astonishing versatility—the onslaughts of disease. The further one goes, the more one realizes that man is organized, not only to do such simple things as to run vigorously, with circulatory adjustments more or less perfect in different performers, but also to meet the varied insults imposed by infections. Man has had a long training in the simple or, better, uniform sorts of circulatory reactions imposed by exposure to heat or cold or by indulgence in hard exercise; and through the ages the five features of the blood and lymph circulation have apparently been adjusted so that the character and limits of their capabilities are reasonably efficient. But as far as disease is concerned, though a certain uniformity of reaction may be expected, there are manifold differences between infections and the reactions they cause; and, as man has developed, new diseases have attacked him. The life of a fish is devoted to three things: he eats; he avoids being eaten; and he reproduces his kind. His diseases are not numerous, since even moderate disability makes him prey for other fish or for lowlier enemies. His habits and his external environment, the sea, are exceedingly uniform.

As the scale of vertebrates mounts to man, the task of getting a living and keeping from dying becomes steadily greater. Man has paid and is paying the penalty of an ever widening external environment—the ability to live under almost any external conditions provided oxygen, water, and food are obtainable. To succeed, he has gained a physiological organization which has increased in complexity as succeeding generations have been able to reproduce and survive. This is an old idea when applied to the extraordinary development of the brain and nervous system in mammals, but the same development has occurred in the simpler matter of the movements and composition of the body fluids.

Something of this sort will answer the question as to why the lymphatic system appears and operates as it does. A docketed, satisfying answer is not for us as yet. All that can be expected is to work away at the picture, which in our time is just blocked out. Our satisfaction and courage rise as each part of the composition is carried toward completion, or as we recognize the appearance of changes more in keeping with new and unforeseen requirements of the external environment.

# II. ESTABLISHMENT AND CHARACTERISTICS OF THE CAPILLARY CIRCULATION


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In 1900, Sir Michael Foster, professor of physiology in the University of Cambridge, England, gave a series of Lane Lectures on the history of physiology. These lectures were the first course published and the little book they grace is a classic of the history of medicine. Foster was the founder of the modern school of English physiology, which has had such a dominant influence from the nineties until today. He combined fine scholarship with a gift for "experiment," though—like Carl Ludwig—his many pupils soon became the tools through which his experiments were done. No one could have been better equipped to lecture on the history of his science.

As was inevitable, Foster gave much space to William Harvey and the discovery of the circulation of the blood and lymph. Of Harvey, he wrote: "The essential feature of Harvey's new view was that the blood through the body was the same blood, coursing again and again through the body, passing from arteries to veins in the tissues, and from veins to arteries through the lungs, heart, suffering changes in the substance and pores of the tissues, changes in the substance and pores of the lungs."[1] The capillaries were the missing link in Harvey's scheme. He knew that somehow or other the blood passed from arteries to veins, but he never saw the marvel of the capillary circulation in the living animal, though this was possible when he announced his discovery.

The compound microscope was invented about 1600 and by 1625 is said to have been used in anatomy. Marcello Malpighi used both simple and compound instruments. He was born in the year of Harvey's publication, 1628, and was the first histologist. In 1661, after having puzzled over

[1] From Foster (1901), p. 47.

the circulation in the lung of the dog, he turned to the frog, where the lung is a sac containing air and where in the transparent tissue, which is the wall of the sac, there is an amazing network of capillaries. Under even moderate magnification this circulation is an astonishing sight, one so arresting that no description ever prepares the observer for it. No wonder Malpighi, after a brief discussion of the problem, breaks his text with the words: "*Magnum certum opus oculi video.*" "I see with my eyes a certain great thing!" He had opened the body of a frog and delivered the lungs, so that their surface might be examined through his microscope. He goes on to say:

"For, while the heart is still beating, two movements contrary in direction though accomplished with difficulty are observed in the vessels so that the circulation of the blood is clearly laid bare; and indeed the same may be even more happily recognized in the mesentery and in other larger veins contained in the abdomen. And thus by this impulse the blood is showered down in minute streams through the arteries, after the fashion of a flood, into the several cells, one or other conspicuous branch passing right through or leaving off there, and the blood, thus repeatedly divided, loses its red colour, and, carried round in a sinuous manner, is poured out on all sides until it approaches the walls, and the angles and the absorbing branches of the veins. . . . . Hence it was clear to the senses that the blood flowed away along tortuous vessels and was not poured into spaces, but was always contained within tubules, and that its dispersion is due to the multiple winding of the vessels."[2]

This short statement established the existence of the blood capillaries.

In spite of contrary opinion and Malpighi's astonishingly modern views as to the significance of other of his discoveries, I doubt if he realized the real physiological significance of what he had seen—that he had found the site of exchange between blood and tissues, the part of the circulation which all other parts were constructed and regulated to serve. But a contemporary, a solid, indefatigable Dutchman, Antony van Leeuwenhoek, not only described the capillary circulation in many different animals but made a good guess at the functional importance of these smallest vessels. In the course of observations upon the capillaries in the dorsal fin of an eel, after estimating their diameter, he remarked:

"Which being considered, we may conclude how exquisitely slender must be the vessels in which the circulation is performed: and if it were not so, how could all the parts of our bodies be continually supplied with nourishment? . . . . And if we reflect, that each of these very small vessels

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[2] From Foster (1901), pp. 96–97. This is a translation from Marcello Malpighi's "De Pulmonibus," Epistola II, in the second volume of his *Opera Omnia,* pp. 141–142.

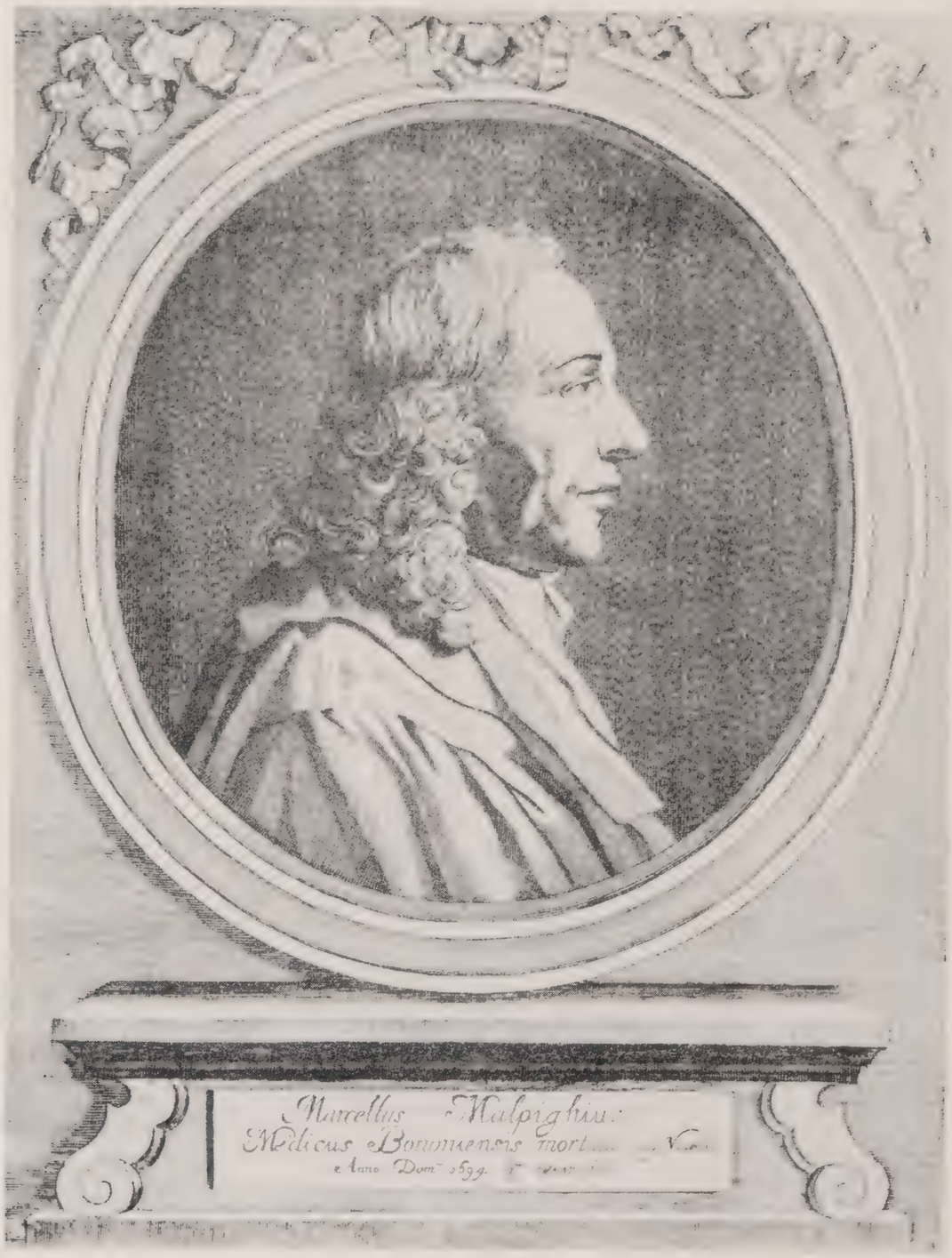


FIG. 7.—Marcello Malpighi, 1628–1694. Frontispiece in his *Opera Posthuma*. Churchill, London, 1697.

must be formed with the same kind of coat as the larger ones though of a thinness proportioned to its size; and farther, if we consider of what wonderfully fine and invisible membranes the coats of the smallest vessels must be formed, and how easily the finest part of the arterial blood may find a passage through those coats, to the end that every part of the body may, from thence, be continually supplied with necessary and suitable

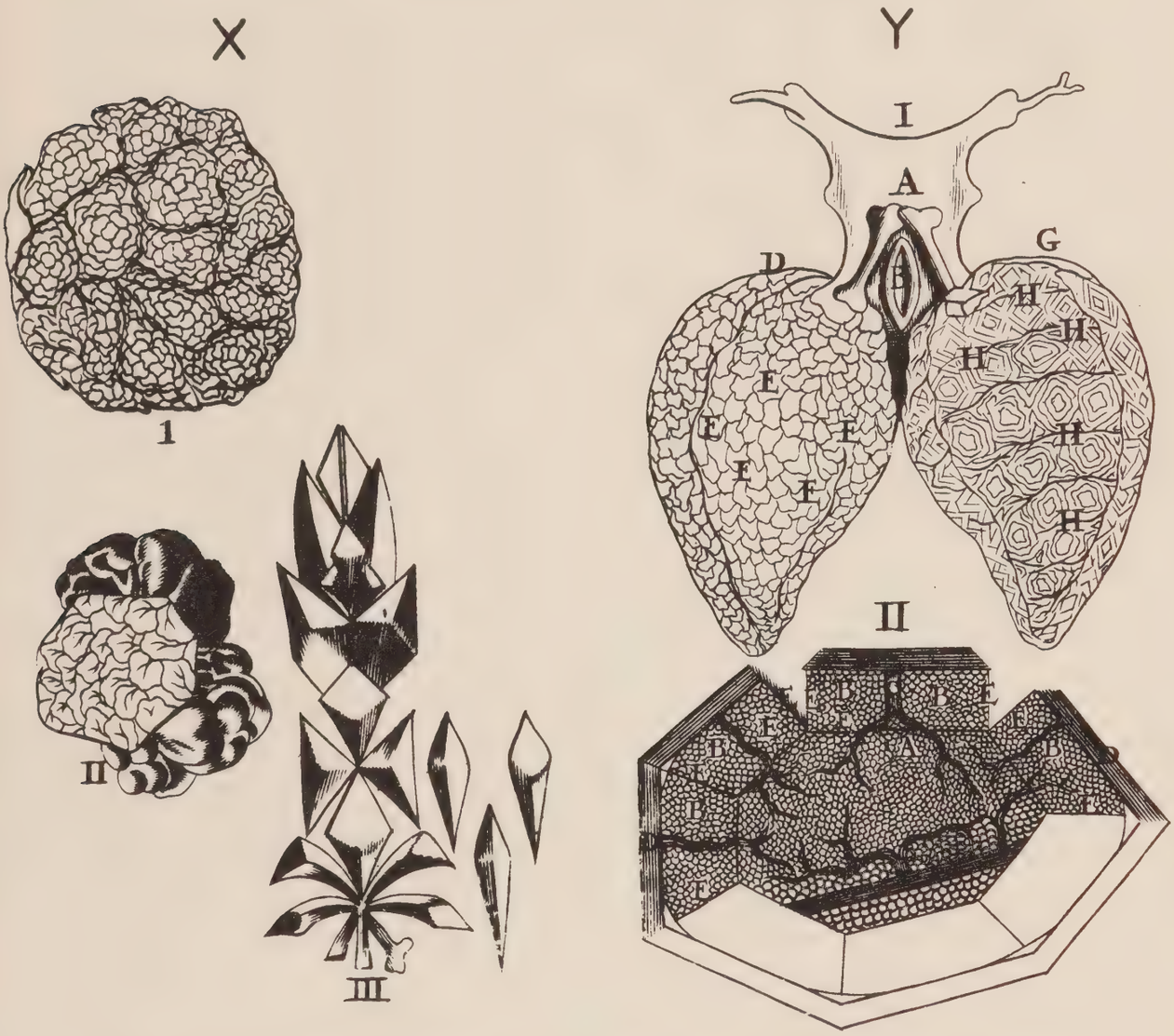


FIG. 8.—*X*, the first illustration of the lung lobule. III is a diagram showing Malpighi's conception of the division and subdivision of the final air spaces in the lungs. *Y*, the lungs of a frog. In the upper sketch (I), *D* is what one sees when the lung, containing air, is delivered from the body; *G*, the opposite lung, has been sliced in two. The lower sketch (II) is an incomprehensible diagram intended to show the subdivision of the air spaces and their relation to the blood vessels. (From M. Malpighi: "De Pulmonibus," Epistolae I and II, *Opera Omnia*, Vol. 2, pp. 133 and 140. Thomas Sawbridge, London, 1686. The illustrations follow p. 144 at the end of the volume.)

nourishment; these things, I say, being duly weighed and considered, it seems clear that the arterial blood, coming from the heart, must contain more subtile and fluid parts than when in its passage to the heart. For the blood will not be deprived of its more subtile juices, while in the larger arteries; to prevent which, I imagine that they are provided with thick and solid coats. And here the particles of blood from which its redness proceeds, swimming in a thin juice, are of a bright red colour; but in the smallest arteries, some of its parts are drawn off for the support and nourishment of the body, whereby the blood, when returning in the veins, being deprived of those thin juices, assumes a darker red, and as more of the thin juices are taken away, it will appear blackish."[3]

Van Leeuwenhoek had many microscopes, and, though simple, not compound, they were apparently better than those of Malpighi. He achieved magnifications up to about 175 diameters, and his numerous illustrations of capillaries, though in the main schematic rather than realistic, are far more satisfactory than the crude sketch with which the Italian accompanied his original description. Van Leeuwenhoek was an engaging figure for any of us, particularly in these days when everyone is so subject to being taught something instead of learning something! He had no university background or connection, nothing to fire his wits save the tinder of a single purpose—to see and describe the invisible world suddenly turned visible by the microscope. His descriptions are as beguiling as is his obvious desire to examine the realities of structure, not the misleading appearances which resulted from poor preparations or from material unsuited to the observations he wished to make.

No honest student of the capillary circulation in the living animal should ever be free from the questions: Am I examining reality—that is, the normal state which would obtain if none of the arrangements for an experiment had been made—or am I seeing extraordinary things engendered by the experimental setting and but distant relatives of the normal conditions I have wished to see and understand? This is no idle warning. The habit of examining fixed, dehydrated, and stained tissues is deeply ingrained. Even as medical students, we begin to think of the microscopic structure of the human interior as stained with hemotoxylin and eosin; and if the slide be marked "normal," what is seen is taken as a certain expression of the living state. The value of dead specimens has been beyond price, but their service is to show the foundations of structure and only occasionally the physiological state of the tissue under examination.

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[3] From *The Select Works of Antony van Leeuwenhoek, Containing His Microscopical Discoveries in Many of the Works of Nature.* Translated from the Dutch and Latin editions by Samuel Hoole, Vol. 1, pp. 100–102. The Philanthropic Society, London, 1800.

FIG. 9.—Antony van Leeuwenhoek, 1632–1723. (From an engraving in *The Asclepiad* by Benjamin Ward Richardson. Frontispiece to No. 8, Vol. 2, facing p. 289. Longmans, Green & Co., London, 1885.) This engraving is one of many made from a portrait by Verkolje in 1695 when van Leeuwenhoek, already famous, was still young both in body and mind.

The last twenty-five years have witnessed a return to the microscopic study of living material, and too often the fascination of the things seen is so great as to hypnotize the observer into thinking he is viewing normal conditions. In a sense he is, for living material separated from its true environment is prone to react in accordance with the new situation. The things observed are usually truly reported; but they do not portray normal states, and not infrequently it is assumed they do. I remember my disappointment in 1926, when Professor Krogh suggested we attempt some direct observations upon the permeability of frog capillaries. I wanted to use the mesentery, but: "No! The circulation becomes abnormal much too rapidly." I saw my destiny, but suggested the tongue of the frog, another tissue so transparent as to permit beautiful definition of the capillaries. Again the answer was, "No! The condition of the tissue changes too fast, no matter how careful one may be." So it became the web of the frog, where the capillaries can be seen less well; but this defect is not so serious as are the errors from observing an abnormal physiological condition when the fact of seeing something extraordinary lulls us into the notion that the "something" expresses normal conditions.

As soon as the tissue of a living animal is displaced from its customary environment, changes occur, and they are particularly marked in the finest parts of the circulation. Hall (1835), one of the first observers of the capillaries in what may be called the modern sense, realized these possibilities of error. At the close of a series of studies upon the frog there is a short section entitled, "Of some Modifications in the flow of the Blood along the Minute and Capillary Vessels," and the last paragraph is a warning as potent today as a hundred years ago:

"In fact I have long ceased to place the slightest reliance upon the circulation as seen in the mesentery, in physiological experiments of any delicacy. The circulation of the web, on the other hand, is unequivocal under judicious management, the arrangement of the toes and of the membrane remaining accurately the same."[4]

There are measurements which cannot be made except upon capillaries probably somewhat abnormal—notably true of examinations of mammalian capillaries requiring the use of high magnification. When such capillaries are examined, the histologist cannot interpret what he sees unless physiological reactions incident upon the experimental conditions are fully realized and their relation to the questions at issue is given due weight. The solution of problems of the circulation by microscopic observation is never easy. Mistakes are most often due, not to inaccurate descriptions of what has been seen, but to the use of these descriptions as evidence of normal condi-

[4] From Hall (1835), p. 71.

tions when in reality they are of abnormal states, most commonly those associated with inflammation.

Van Leeuwenhoek was essentially an observer of living things, and to those attempting direct observations of the capillaries nothing can be more wholesome than his simple account of trials and difficulties as he went from animal to animal in order to gain the view he was sure was wait-

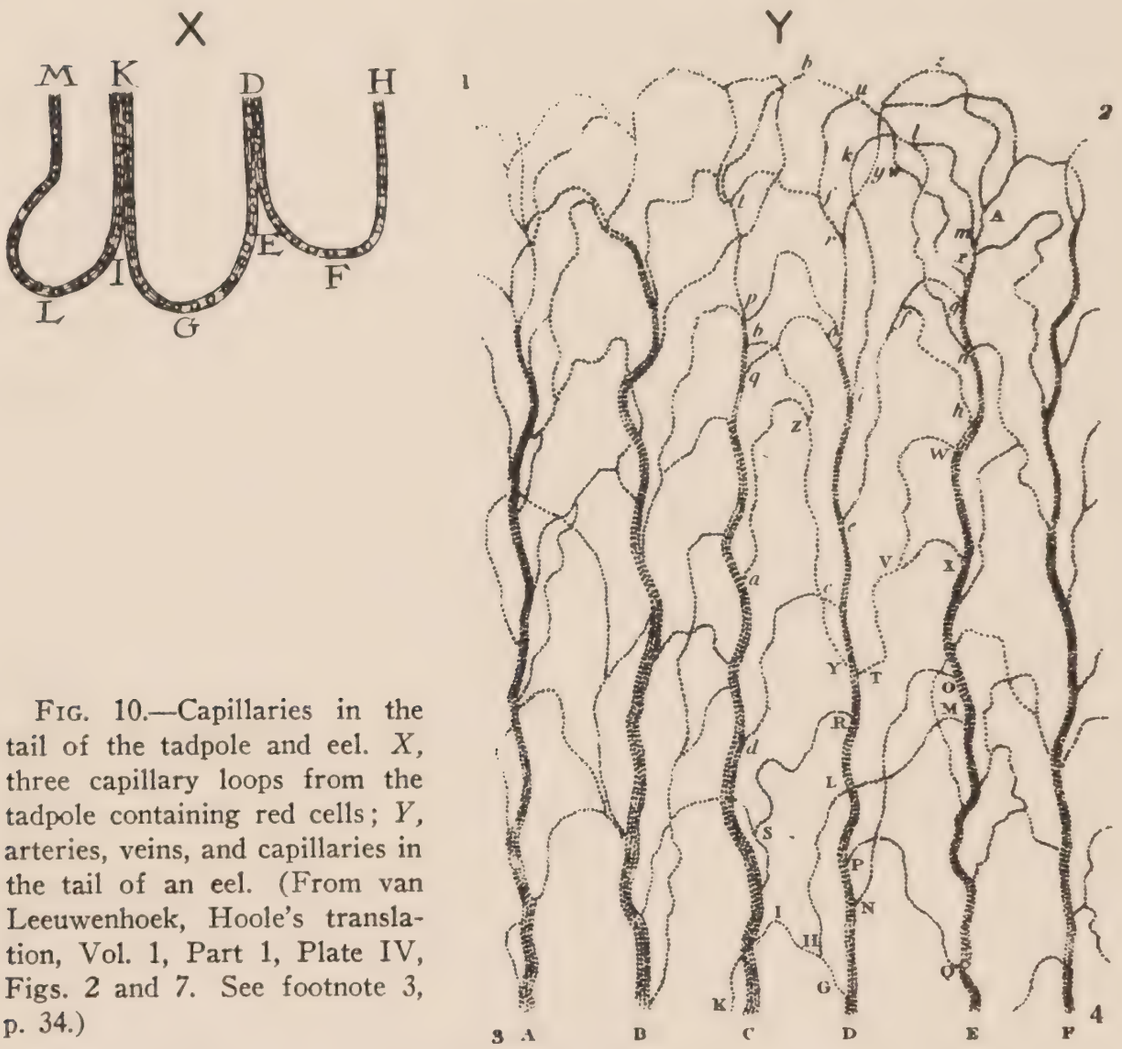


FIG. 10.—Capillaries in the tail of the tadpole and eel. *X*, three capillary loops from the tadpole containing red cells; *Y*, arteries, veins, and capillaries in the tail of an eel. (From van Leeuwenhoek, Hoole's translation, Vol. 1, Part 1, Plate IV, Figs. 2 and 7. See footnote 3, p. 34.)

ing for him. First he selected "the comb of a young Cock," then the ears of "white Rabbits." Next, he says, "my greatest expectation of success, was placed on a Bat." But the wing membrane was too opaque to give real satisfaction; and then came the tail of the tadpole, where for the first time the real nature of the capillary circulation became apparent (Fig. 10, *X*). Amongst the tadpoles collected for him, there were a few very small fish whose tails displayed a promising group of capillaries which could not be watched satisfactorily since "this fish did not long continue quiet." Finally, he secured eels "not longer than one's little finger," and

these not only showed many capillaries in the tail but—contrary to my own experience with eels—kept quiet long enough to permit drawing the vessels. The result is found in Figure 10, *Y*; and this, I think, is the first recognizable delineation of the capillaries as we know them today. To both Malpighi and van Leeuwenhoek the capillaries were simply tubes capable of retaining blood, as judged by the behavior of the red cells. Neither investigator gave any conception of their structure, though the deductions of van Leeuwenhoek as to function carried implications as to the physiological needs fulfilled via the capillary walls.

Van Leeuwenhoek died in 1723, and for a little over a hundred years the capillaries were subjected to occasional speculation but little real observation. It was an unhappy century, culminating in the rise and fall of a dictator, a cosmic episode which occurs periodically and is invariably highly unpleasant for the world and eventually for the dictator, but not until experimental science has suffered woefully. Such periods are particularly disastrous for medicine, since all emphasis is toward the application of what is known and not toward gaining new knowledge. In spite of every handicap, here and there brilliant performers always appear. During the period between van Leeuwenhoek and 1820, the foundations of respiratory physiology were laid, and the edifice would perhaps have risen higher had not Lavoisier been compelled one day to meet the invention of that gifted practitioner, Dr. Guillotin. In 1801, Bichat made the capillaries into a sort of separate system. He believed the heart had no influence upon the blood in the capillaries, which in some way moved the blood on to the veins; but he did not study capillary structure, and it was not until 1839, when Schwann described nuclei in the capillaries of tadpoles, that the supposedly homogeneous capillary wall fell into line with the cellular construction of other tissues. Schwann's record of this discovery is found in Figure 11, and is obviously a very poor picture of a very important fact.

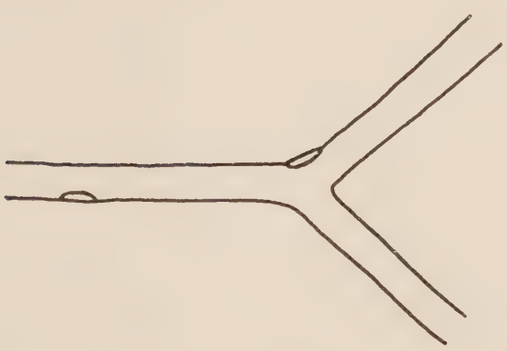

FIG. 11.—The first drawing of nuclei in the wall of a capillary. (From Schwann, 1839, Plate IV, Fig. 11, following p. 92.)

Almost thirty years later Hoyer (1865), using the method of silver impregnation, demonstrated the borders of the endothelial cells in the blood vessels; and this discovery made the simple tubes of van Leeuwen-

hoek conform completely to the cell theory. It seemed as if the problem of capillary structure were finished. But structure is merely bait for the physiologist, and he is not happy until function is safely on the hook. Ever since the capillaries were discovered, men here and there had seen them change in diameter or appear where no vessels had seemed to exist (Stegemann, 1927). This experience, a commonplace of today, was possibly so much dependent upon crude microscopical equipment that a number of years passed before changes in capillary diameter were recorded with so much certainty that the capillaries attained a measure of the independence Bichat had guessed for them, and had elaborated in a tedious discussion none too creditable to his clear head. This course of events is almost invariable in medicine. When insulin was discovered, I can well remember that the classical experiment of Banting and Best was proposed a year before by a third-year medical student and rejected by all of us in the laboratory as too much of a task for a man with no experience in animal work. Later, when the medical world appreciated the significance of insulin, it developed that several persons had perhaps secured the same substance a few years before, but had not realized the meaning of what had been found. New things, new ideas, new views are of little use until they come to us through someone who describes them reasonably well, and who, if his vision goes farther than the intellectual horizon of the day, adds to his experimental achievement the import of this addition to man's welfare.

It was 1865 when Stricker saw contractions of capillaries in the excised nictitating membrane of the frog. He wrote two papers describing capillary contractility, and later was one of the discoverers of the dilatation of arterioles and capillaries resulting from stimulation of sensory nerves, a discovery recognized long after by Bayliss (1900–1901) as fundamental for explaining the vessel widening which is such an essential part of inflammation.

But Stricker's findings made no impression, and when Rouget (1873) not only reported the contraction of capillaries but made drawings of spider-like cells plastered on the outside of the endothelium, which he said constricted the vessel, he too passed unnoticed. Indeed, Rouget would hardly be a name in modern physiology had not Steinach and Kahn (1903) described and pictured the contraction of capillaries in the nictitating membrane of the frog (Fig. 12, *1, 2, 3,* and *4*), and at the same time reproduced Rouget's drawings of the extra-endothelial contractile cells (Fig. 12, *5* and *6*). Figure 12 is a classical illustration in physiology, and shows that capillary contraction can be due to folding of the vessel wall. This behavior of the capillaries in the nictitating membrane has been seen frequently, and Krogh at first believed that capillaries depended almost entirely upon these specialized extravascular elements, which he called Rouget cells, for

regulation of their diameter. This contention was too much for many histologists, who, though they sometimes saw and pictured such cells as Rouget had described, did not venture far as to their function and preferred to think of the blood capillary as a passive affair, narrow or wide in accordance with the blood supply of the moment. Steinach and Kahn not only showed that capillaries may change in diameter, but they measured these

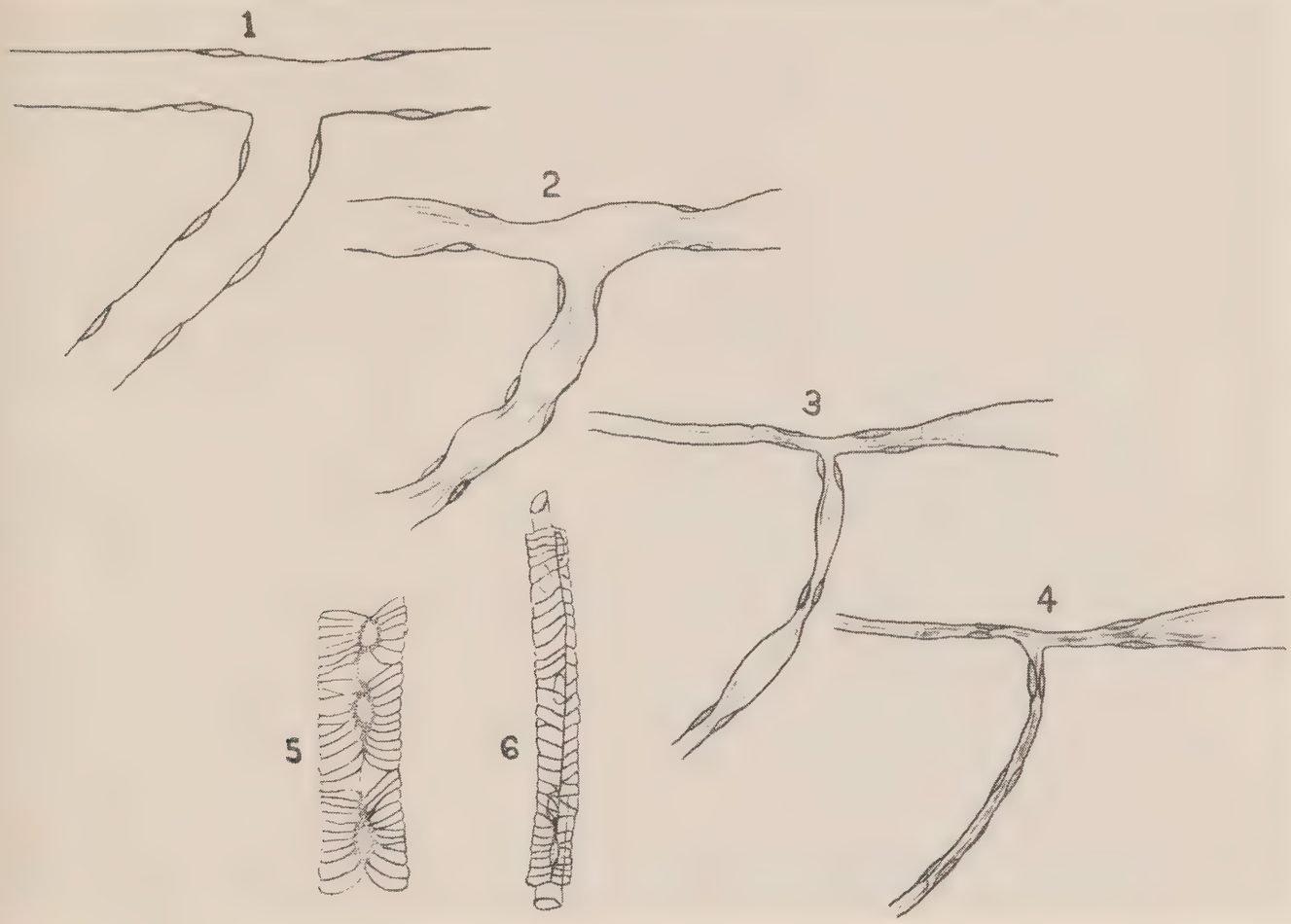


FIG. 12.—The stages in capillary contraction observed by Steinach and Kahn in vessels of the nictitating membrane of the frog. The large capillary, *1*, slowly becomes the fine strand seen in *4*. The longitudinal folding of the tube is obvious. Drawings *5* and *6* are taken from Rouget, 1865, and show the extravascular cells believed to accomplish the folding. (From Steinach and Kahn, 1903, Plate II, Figs. 1, 2, 4, 5, 6, and 7.)

alterations in terms of the outside diameter of the vessels; and since this was progressively less, as is easily seen in Figure 12, they attributed the change to influences operating from outside the endothelium rather than to swelling or to actual contraction of the endothelial cells.

In the period of these first direct observations and until 1922, there appeared a number of experiments which confirmed the fact of capillary

contractility without much reference to the way in which it was brought about. Krogh (1922; 1929) summarized this evidence, together with his own observations, and left no doubt that the capillary circulation in many parts of the body was not merely subservient to cardiac activity and the conventional effects of arteriolar change mediated through vasomotor nerves, but was to a fair degree an independent entity. This meant that, in the face of need for increased blood supply, not only was there a series of what, in terms of the whole organism, we may call cosmic reactions which shifted blood to the active tissues, but also in the tissues themselves a reaction occurred assuring the success of the cardiac and vasomotor activities which provided more blood. Of what use is an increased rate and force of the heart and a heightened blood pressure if the tissue, suddenly active, retains a total capillary surface adjusted to the moderate requirements of quiescence? It is logical to expect not only that, under the necessities of increased work, the tissues engaged should be provided with more blood through central ordering of the mechanism for delivery but also that the distribution of capillary blood in the active tissue should become as wide as possible. This is exactly what should happen, and it is exactly what does happen. In 1919, Krogh (1918–1919) found that working muscles received more oxygen than could possibly be accounted for by the extent of the capillary surface thought to be available for oxygen diffusion. There could be but one answer, namely, the enlargement of the capillary bed in accordance with the new requirements of the tissue.

I need not go through the many experiments which converted what was a mathematical essential into observed fact. The actual figures are of no importance, since they necessarily vary from animal to animal. It was the degree of difference which enforced conviction, and thus twenty-two years ago there came another large verification of Claude Bernard's principle! If active cells are to perform persistently and successfully, the environment in which they labor must not suffer serious change, or activity will cease or become inadequate. The muscles of the oarsman and the runner must perform in a medium as nearly that of rest as possible. If increased oxygen and other needs are to be met, an immensely increased blood supply must not only be provided but must be made available through extended avenues of distribution. When activity is over, the widening of capillaries and the opening of vessels previously shut are no longer necessary, and the tissue slowly returns to a smaller number of capillaries conducting blood, and the individual vessels are of less diameter.

The contraction and dilatation of capillaries by longitudinal folding of the wall is a type of change in diameter which possesses certain obvious advantages. Widely dilated capillaries, such as are seen in areas where obstruction of veins has been of some duration and the arterial pressure

normal, leak fluid rapidly, and there is a general impression that increased capillary diameter means increased permeability of the wall. If dilatation is accomplished by unfolding, there can be no question of stretching and thinning of the endothelium until the unfolding is finished, and the final caliber of the vessel is determined by the tone of the wall under the environmental conditions of the moment. If capillary pressures are great enough to cause further widening, it can then be accomplished only by stretching of the endothelium, and there are reasons for believing that stretched films of protein display rapid increase in permeability.

There is no doubt that capillary endothelium possesses that vague but important entity called tone, a physiological quality seen so prominently in smooth and striated muscle, where it means ability to function at different initial lengths. Tone of capillaries is exhibited in ability to contract and dilate, even though the vessels have been sustained at different diameters for long periods. It is easily confused with elasticity, which is also a property of capillary endothelium and is very marked in the finest lymphatics, which have never been shown to have independent contractility but which may be widely stretched by increased internal pressure and when this is released return to normal diameter.

The experiments of Krogh and his pupils reintroduced physiologists to the capillaries. In the minds of most readers of the many papers which resulted, there was no doubt about the adaptive nature of the capillary bed; but while it seems today that the capillaries have been found to behave as has been indicated, a number of histologists and physiologists did not believe in the idea of independent changes in the capillaries, and particularly in the manner in which such changes were said to be accomplished.

Three views were expressed:

1. Capillaries were elastic structures which opened or dilated and later returned to normal diameter quite passively, the extent of the capillary bed being determined by cardiac output and arterial and venous pressure. This was a retention of the old idea of circulatory regulation, which grew up following the discovery of the vasomotor nerves and the nervous regulation of the heartbeat. The supporters of this limited conception of circulatory regulation have grown steadily fewer, and the idea of a universally passive capillary circulation faces, with profit, a prospect of extinction.

2. There were those who believed, as Krogh first presented the case, that extravascular cells, with characteristics resembling smooth muscle and with vasomotor innervation, were responsible for constriction.

3. Finally, and nearest the truth, were and are those who have realized that capillary contraction may be due to outside elements, such as the Rouget cells, and also to changes in the endothelium independent of all other cells.

Field (1935) found in frogs and rats that both mechanisms for contraction and folding and also swelling of endothelium could be seen, and might be present simultaneously in vessels in the same tissue. Figure 13 is an illustration of capillary contraction due to electrical stimulation of capillaries in the nictitating membrane of the frog. The caliber of vessel *B* has been altered by folding and also by swelling of endothelial nuclei.

At the present time one cannot say which of these mechanisms is most important. The fact that capillaries change with tissue needs is what is of consequence. This fact realized, it is not surprising that active contraction

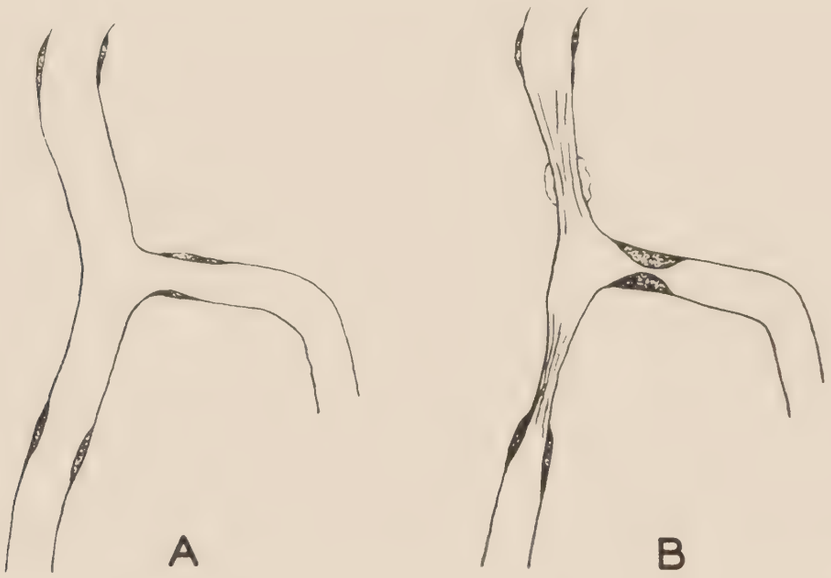


FIG. 13.—*A*, normal capillaries in the nictitating membrane of the frog; *B*, capillaries showing narrowing following electrical stimulation, and accomplished both by folding of the membrane and by swelling of endothelial nuclei. (From Field, 1935, Fig. 3, p. 183.)

and dilatation have been found in the capillaries of organs subject to marked fluctuations in metabolic rate. No one can be surprised at adaptive changes in the capillary circulation of voluntary muscle or of the kidney, where alterations in functional performance are so frequent and require immediate increase in blood supply. In contrast, the lungs possess an enormous system of capillaries, which exists to provide oxygen for accessions of metabolism in other parts of the body. If the lung capillaries are observed under good conditions, changes in capillary diameter and flow through areas previously containing little blood appear a passive affair, with the capillary surface increased and decreased in accordance with the output of the heart.

Capillary contraction and dilatation adapted to the needs of the tissue are conspicuous in the skin, in muscle, in the kidney, and, as has been

pointed out, can be found wherever sudden and extensive changes in blood supply are required. The organism possesses what Meltzer called a "margin of safety," which is expressed in many ways—among others, in the inherent arrangements for blood supply. When more oxygen and more fluid containing essential solutes are needed in order to meet the physiological requirements of high and rapid performance, the capillaries in the organ or part dilate. If this emergency extension of capillary surface persisted during periods of functional quiescence, we should have a sort of physiological extravagance which nature is prone to avoid. The fundamental nature of relaxation is a more obscure phenomenon than is contraction; and a receptive type of relaxation, such as the capillaries apparently possess, is far more mysterious than the type of relaxation which follows a twitch of voluntary muscle. Changes in capillary diameter are probably mediated chemically; and relaxation of the capillary, with increased diameter, is perhaps more important than contraction in that it is the essential companion of calls for work or for reaction against an irritant. Prolonged contraction of capillaries is uncommon. Under ordinary circumstances, after capillary relaxation becomes unnecessary, as upon the cessation of work, contraction slowly follows, so that the capillary bed is adjusted to the resting state of the tissue.

I cannot enter the problem of the varied conditions which induce changes in capillary diameter. Had I the courage to attempt such a task, there would be no end to it. In any case, why does this matter of capillary change enter the subject of these lectures? The issue which concerns the lymphatic system rests finally with the fact that blood capillaries carry a load of blood adapted to the immediate supply of metabolic needs. Oxygen is of course the greatest of the requirements imposed by work, but there is no doubt that the fluid environment of the active cells must also be held uniform, or as nearly so as possible, and this is apparently brought about by a more rapid formation and movement of extravascular fluid. Oxygen brought to working muscle in increased amounts is used or remains in the blood combined with hemoglobin, but water and dissolved substances which leave the capillaries continuously must not accumulate in the tissues, since the "internal environment," the tissue fluid, is held as closely as possible not only to uniformity in composition but also to uniformity in volume. During activity of many parts, swelling occurs, due in the main to increased blood in the vessels of the working tissue. A residuum of this swelling may remain after work has ceased, particularly in a tissue such as voluntary muscle where activity is terminated abruptly. This residual swelling is the expression of increased escape of water from the capillaries, and disappears with fair rapidity during rest.

That an increased heartbeat and blood pressure accompany increased

functional activity is axiomatic. It has usually been thought that the capillaries were safeguarded against undue pressure and consequent abnormal leakage of fluid from the blood by constriction of arterioles. A little consideration will suffice to indicate that, while such a method of keeping capillary pressure within bounds might succeed in doing so, it would at the same time tend to reduce the volume of blood reaching the capillaries to a point below the needs of the working cells, and thus defeat the adjustment so urgently needed.

There is another arrangement, really part of the capillary circulation but perhaps a stage nearer the arterioles, which is vitally important for permitting a maximum supply of blood to the capillaries and at the same time for checking the development of excessive capillary blood pressure. This factor is the system of arteriovenous anastomoses which have been found in many different tissues but which, until recently, have not been related to function as clearly and emphatically as they deserve. Hoyer (1877) not only gave the first really satisfactory description of arteriovenous anastomoses but accompanied his paper with a history of the earlier descriptions of these curious connections, and finally ventured a series of shrewd guesses as to their function. He says, for example: "There can be no doubt that any connection [between arteries and veins] acts as a sort of shunt or safety-valve which protects the circulation against major stresses, and is especially effective in regulating the capillary circulation in certain regions."[5]

It was many years before Hoyer's findings were rediscovered—a type of occurrence very frequent in physiology. For a long period, regulation of the peripheral circulation was examined and thought of in terms of the vasomotor control of the arterioles and the force and frequency of the heartbeat. During this time the capillaries emerged slowly from a passive to an active role in the regulation of blood supply; and finally the realization that something more was needed, if the capillaries were to be fully used and, at the same time, protected from undue pressure, came slowly out of obscurity through report after report upon the existence of arteriovenous connections.

These anastomoses open and close more readily than the capillaries. If living tissue is under observation and the real conditions of the experiment are not realized, they may form so prominent a part in what is seen as to lead to the idea that they, not the capillaries, are the essential part of the peripheral circulatory system. For example: When the frog mesentery or, even worse, the mesentery of a mammal is drawn out of the abdomen and arranged for microscopic examination, the circulation rapidly becomes that seen during inflammation. The capillaries dilate and more blood moves

[5] From Hoyer (1877), p. 632.

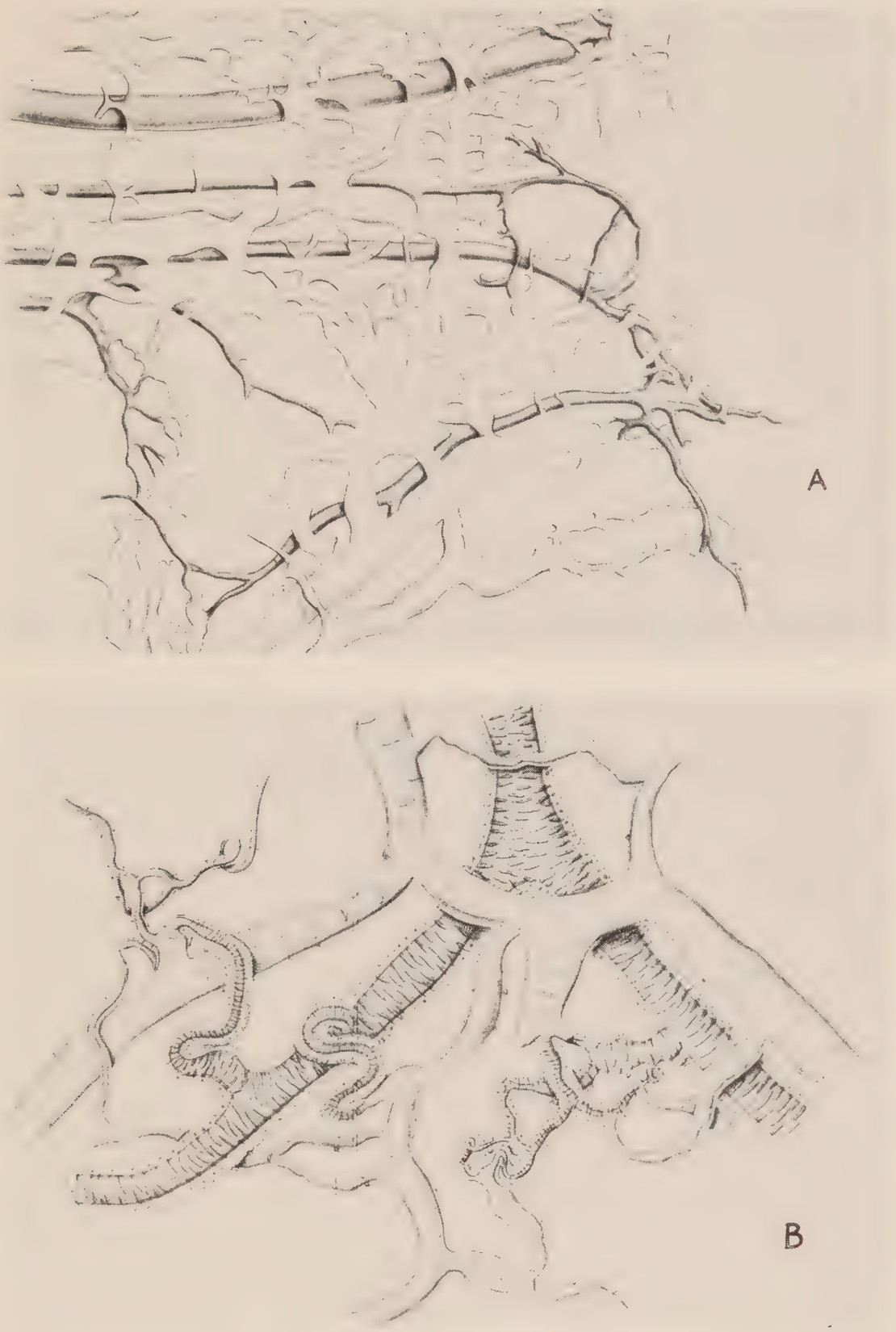


FIG. 14.—Arteriovenous anastomoses. *A*, the circulation in the nasal mucous membrane of the rabbit. Arteries black; veins clear. At several points there are direct connections between the arteries and the venous net. *B*, the circulation in the tip of the tail of the cat. Arteries black; veins clear. Arteriovenous anastomoses large and easily seen. (From Hoyer, 1877, Plate 38, Figs. 3 and 4, preceding p. 603.)

through the tissue. It is soon noticed that short cuts between the arteries and veins are a prominent part of the picture. This is all quite true and thoroughly appropriate to a description of inflamed tissue, but not to the state of the circulation in a normal, undisturbed part. The anastomoses have a saving role in many situations requiring circulatory adaptation to meet either the necessities of normal activity or those imposed by onslaughts from without, such as irritants causing inflammation. They are a beautiful addition to the machinery for regulating the capillary circulation. Their function is to provide maximal blood flow through the capillaries without permitting undue pressure. They oil the machinery involved in capillary function, and must not be thought of as the machine itself.

All of the characteristics of capillaries so far described have dealt with what are usually thought of as "typical" vessels, such as are found in the skin, muscle, and mucous membranes and in a number of highly specialized organs—pancreas, salivary glands, etc.—but this is by no means the whole story. The capillary circulation has one purpose: to serve the needs of the tissue in which it operates. One cannot, therefore, be surprised if here and there the structure of capillaries is not at all in accord with that which has been described but is specialized for certain requirements not easily met by the conventional structure.

A few examples will serve for illustration. The liver has two sources of blood: the hepatic artery, which is essentially for oxygen supply; and the portal vein, which brings the raw material upon which the liver works. The portal blood is under low pressure, and is widely distributed through vessels of the nature of capillaries but so large and with walls so ill-defined as to have gained another name—"sinusoids." There was a time, and that not so long ago, when the blood in these vessels was thought to be directly in contact with the liver cells, there being no true endothelial lining. This conception, which arose from inadequate methods of examination, no longer holds ground. Capillaries may vary structurally in different organs, but an endothelial lining sooner or later has been found, so that even in the spleen, that last refuge of the "open vessel" conception, the closed capillary is apparently established, and the whole system thus operates upon the general principle of a continuous but variably permeable endothelial lining. The liver sinusoids or capillaries are examples of vessels of extreme permeability, so much so that injection masses delivered via the portal vein reach and enter the liver cells. This means, not lack of endothelium separating blood and cells, but—as improved observation has demonstrated—simply a membrane of extreme delicacy. There is other evidence of free permeability. Liver lymph is readily collected and often in large amounts. In ten dogs the protein concentration of the blood plasma averaged 5.74 per cent and liver lymph from the same animals 5.58 per cent (McCarrell, Thayer, and

Drinker, 1941), an identity of composition which is remarkable and a concentration of protein in lymph higher than is obtained from any other source.

In contrast to the liver sinusoids, capillaries in other regions permit the filtration of water and salts alone. For example, the glomerular capillaries in the human kidney provide protein-free urine. This tightness of the glomerular capillary filter is not found in all mammals. The white rat normally loses protein in the urine, and the orthostatic albuminuria of man is an expression of the narrow margin which exists between retention and loss of protein by the glomerular capillaries in human kidneys free from disease. The physiologist must always try to account for findings of such distinctive character, and turns first to structure to gain his answer. This resource is not necessarily satisfactory but is at least a temporary solace against the urge which often interferes with the sleep of such unfortunate fanatics. In the case of the glomerular capillaries, there is a structural peculiarity, the fact that the capillary loops possess walls with two layers of cells, endothelium reinforced by epithelium. It is of interest that a similar sort of two-layered structure is found in the capillaries which filter out the cerebrospinal fluid and in those of the aqueous humor, and in both cases there is little or no escape of protein.

The subject assigned me is "The Lymphatic System," and I can readily believe that so much attention to the blood capillaries may appear foreign to my real task. If such an impression has been created, it is because of failure to say clearly what is a strong conviction. Lectures on the lymphatics alone would be confined in the main to descriptions of structure and distribution of vessels. The minute the question as to why we have lymphatics is asked, function takes the foreground, and function of the lymphatics cannot be isolated from that of the blood capillaries. Both serve the same end—the maintenance of the internal environment at constant composition and volume. Where, as in mammals, most of the capillaries leak blood protein, the lymphatics return most of it to the blood. They are a means of restraining one cause for accumulation of water in the tissues and for holding the effective osmotic pressure of the plasma proteins at the highest possible level, so as to bring about reabsorption of water by the blood capillaries. They play a part in infection and in the removal of foreign materials; but the real usefulness of the lymphatics is nearly always to supplement reactions initiated in the blood capillaries and later in certain respects regulated through lymphatic absorption. They are functionally distinctive, but as part of a larger process—soldiers in an army whose individual performances may be arresting, but whose real accomplishments are inseparable from those of the army as a whole.

# III. APPEARANCE AND ELABORATION OF LYMPHATIC VESSELS

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There are few people even today who have ever really seen lymphatics, and usually even such persons have had to be content with a fleeting view of none save the most conspicuous parts of this vasculature. To this cloudy experience much must be added through faith, particularly if those concerned are active practitioners of medicine. There is an undercurrent of conviction that the widespread and vaguely visualized lymphatic system is of vital consequence in the progress of disease, a conviction, of course, correct but intelligible only when the lymphatics are studied directly in the living animal.

No one with experience can think it strange that the lymphatics were discovered in a large mammal, the dog, and that their discovery was made in the years when Harvey was lecturing on the circulation, though he had not published his observations and conclusions. It was a time of beginning skepticism in medical matters. The Aristotelian and, more so, the Galenical pronouncements as to the movement of the blood and the functions of the vessels attached to the heart were meeting whispered rebellion. Here and there men realized how mistaken must be conceptions of function drawn from examinations of dead bodies. Harvey knew that the most careful anatomizations could tell certain facts of structure. But he also knew that the structures one saw were the parts of the machine, not the integrated working of the living body.

I cannot refrain from a striking example of what might have advanced medicine almost a hundred years, had another superb intelligence turned from studies of the dead to studies of the living. Leonardo da Vinci lived from 1452 to 1519. Harvey's observations and conclusions were published in 1628, though he knew the facts eleven years earlier and lectured upon them prior to the appearance of his book. From time to time, students of Leonardo, carried away by his astonishing versatility and originality, en-

deavor through his notes and the drawings of innumerable dissections to show that he understood the existence of the circulation long before Harvey grasped the fact and initiated a new medicine. I think that had Leonardo turned from the countless corpses he dissected to even a small number of observations upon living animals, he might have decribed the circulation; but he was restricted by wide knowledge of ancient authors, upon which he piled an extraordinary amount of personal observation. He knew as much or more anatomy than Vesalius, who was born five years before Leonardo died; and it is said Vesalius borrowed from him. The mechanistic mind of Leonardo could not relinquish authority. It is a misfortune that those who apply the idea that living creatures are but complicated expressions of the natural laws which they slowly learn from studies of inanimate objects, measure the reactions of living things with a rod whose every mark is stamped with the authority that can be established for nonliving material. This is a state of mind easy to understand, one I have often encountered in high-powered physicists, particularly in young specimens, who do not realize that the great majority of physiological conclusions must be tempered with judgment—judgment which does not involve the recorded data alone but does involve most emphatically the state of the living tissue upon which the disturbing conditions of experimentation must be imposed.

In Leonardo's day, if Galen or even Mondinus had said it, the fact was fact before one's eyes; and this was particularly so in the case of Leonardo, who set himself the task of correlating an immense knowledge gained from his foul corpses with ancient pronouncements as to function—pronouncements which were wholly visionary and which would have become evident as such to him had he but looked at the living instead of the dead. Leonardo did record one experiment on the movements of the heart during the slaughtering of pigs; but it was a trivial effort and infinitely wide of the issues so clearly seen and analyzed by Harvey in living animals. Recollect the first sentence in the first chapter of Harvey's book:

"When I first gave my mind to vivisections, as a means of discovering the motions and uses of the heart, and sought to discover these from actual inspection, and not from the writings of others, I found the task so truly arduous, so full of difficulties, that I was almost tempted to think, with Fracastorius, that the motion of the heart was only to be comprehended by God."[1]

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[1] From William Harvey's "An Anatomical Disquisition on the Motion of the Heart and Blood in Animals," 1628, in *The Works of William Harvey, M.D., Translated from the Latin with A Life of the Author* by Robert Willis, p. 19. The Sydenham Society, London, 1847.

In Harvey's time, when men were in one of those rare periods where thinking individually, not as authority told them to think, became pandemic in the small world of culture, it was natural that men of his fiber should appear here and there to tell their many curious listeners new things and new views. Sometimes these novelties were highly unpopular with those whose command of human conduct led them to believe that nature herself must conform to some worn-out tenet of human origin.

In 1622, Gasparo Aselli was professor of anatomy and surgery in Pavia, a city not far south of Milan and though of diminishing consequence still of importance, so that Aselli must have been an able practitioner or he would have had no such post. Aselli has the credit for the discovery of the lymphatic system, accorded to him for his description of the lacteal vessels in the mesentery of a dog. There is no question that these lymphatics so conspicuous in a well-fed mammal had been seen and mentioned long before (Herophilos, 300 B.C.; Erisistratos, 250 B.C.); but Aselli not only saw the lacteals, he was enthusiastic about what he saw, and enthusiasm is a powerful force in directing the eyes of one's fellows. Aselli's description of the discovery of this new set of vessels, which contained not blood but milky fluid, is almost as famous as the fact of seeing them, and still loses nothing through repetition. It is as follows:

"On the 23rd of July of that year (1622) I had taken a dog in good condition and well fed, for a vivisection at the request of some of my friends, who very much wished to see the recurrent nerves. When I had finished this demonstration of the nerves, it seemed good to watch the movements of the diaphragm in the same dog, at the same operation. While I was attempting this, and for that purpose had opened the abdomen and was pulling down with my hand the intestines and stomach gathered together into a mass, I suddenly beheld a great number of cords as it were, exceedingly thin and beautifully white, scattered over the whole of the mesentery and the intestine, and starting from almost innumerable beginnings. At first I did not delay, thinking them to be nerves. But presently I saw that I was mistaken in this since I noticed that the nerves belonging to the intestines were distinct from these cords, and wholly unlike them, and, besides, were distributed quite separately from them. Wherefore struck by the novelty of the thing, I stood for some time silent while there came into my mind the various disputes, rich in personal quarrels no less than in words, taking place among anatomists concerning the mesaraic veins and their function. And by chance it happened that a few days before I had looked into a little book by Johannes Costaeus written about this very matter. When I gathered my wits together for the sake of the experiment, having laid hold of a very sharp scalpel, I pricked one of those cords and indeed one of the largest of them. I had hardly touched

it, when I saw a white liquid like milk or cream forthwith gush out. Seeing this, I could hardly restrain my delight, and turning to those who were standing by, to Alexander Tadinus, and more particularly to Senator Septalius, who was both a member of the great College of the Order of Physicians and, while I am writing this, the Medical officer of Health, 'Eureka' I exclaimed with Archimedes, and at the same time invited them to the interesting spectacle of such an unusual phenomenon. And they indeed were much struck with the novelty of the thing."[2]

Aselli, as is not infrequent in medicine, stuck to his discovery and did not, at least so far as is known, risk his reputation upon other physiological ventures. He died four years after his great day with the well-nourished dog and his appreciative friends, two of whom saw to the publishing of his book, *De Lactibus sive Lacteis Venis,* which has become a great rarity in collections devoted to medical history. There is not much in this little book beyond the description of the lacteals and of the fact that they are valved to hinder back flow and a demonstration of the large lymph node seen so prominently in the dog and still called the pancreas of Aselli. Unfortunately, Aselli was a thorough Galenist and believed his new vessels carried material to the liver to be "concocted" into blood. It has been my experience that modern workers upon the lymphatics are good friends and good fighters. Such was the case at the beginning or else this first account must have awaited another hand.

Not only was *De Lactibus sive Lacteis Venis* published by Aselli's friends, but it was the first book to contain successful colored anatomical drawings. There had been previous attempts, but the four polychrome woodcuts which illustrate Aselli's book will always speak for him and for themselves. Figure 15, an engraving from Aselli's original, is perhaps the best of the group, and shows the white lacteals running to *L*, the large node Aselli thought another pancreas. From this node he believed the lymph went to the liver, a statement uncorrected until the discovery of the thoracic duct.

Figure 16 is the engraving of Aselli which appears at the front of his book and beneath which his friends placed a Latin couplet. This couplet, after a long struggle, proved too much for the medical Latinists of Boston. Mrs. Drinker and I fell first and called in the "shock Latinists," Drs. Frederick B. Lund and Frederic T. Lewis. Eventually—and in military parlance—"having attained all our objectives," that is, being quite sure of the meaning but unable to put it into words, we turned to our Harvard Roman, Professor Edward K. Rand, in Cambridge with the following result: "This

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[2] From Foster (1901), p. 49.

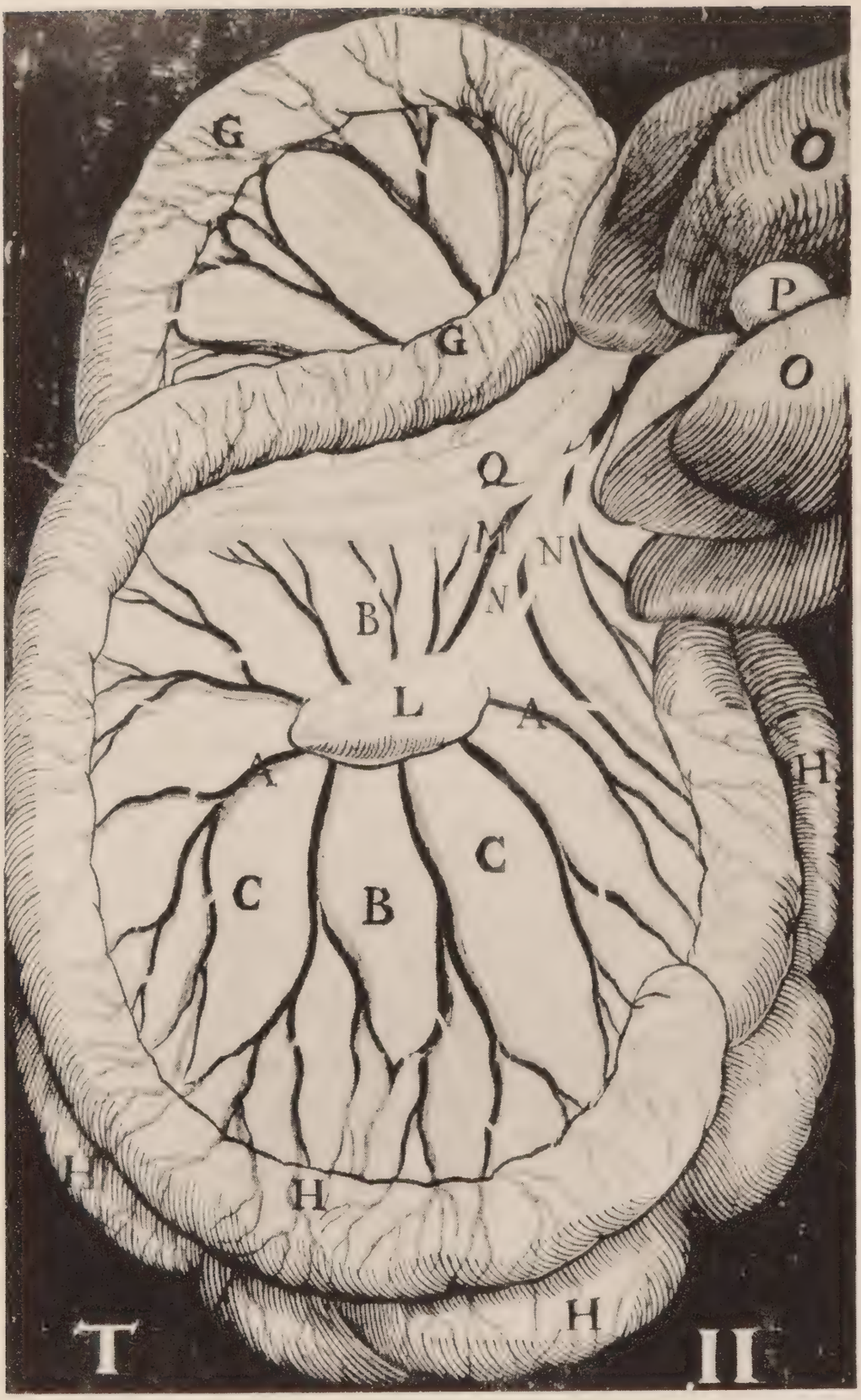


FIG. 15.—The small intestine, *G*, pancreas, *Q*, and related structures in the dog. The white lines are lacteals running in the mesentery from the bowel to the large lymph node, *L*, the so-called pancreas of Aselli. The multilobed dog liver is seen in the right upper corner. (From Aselli, 1627, Fig. 2, preceding p. 1.)

FIG. 16.—Gasparo Aselli, 1581–1626. The discoverer of the lacteals. (From Aselli, 1627, frontispiece.)

is the face of Gaspar: The right hand of Galen has more renown; his [Gaspar's] was not less sure."[3]

Not long after Aselli, whose findings made little impression against the roar of the battle which followed Harvey's publication, a French physician, Jean Pecquet, in 1651 described the receptaculum chyli and the thoracic duct. Historically Pecquet hails from Dieppe; but he was a lusty soul who practiced here and there in France, with a natural predilection for Paris, where, according to Stirling (1902), he died in 1657 from an overdose of brandy, which—and this was not a unique opinion—he thought a universal panacea.

At one time Pecquet was an ardent dissector, and in 1651 he published his *Experimenta Nova Anatomica.* Fortunately, this short report was translated and appeared in English two years later. Pecquet begins by commending Aselli for his discovery of the lacteals, and mentions others who have believed that the lacteal fluid goes to the liver or have failed to find the real pathway. Then follows a brief summary of the new facts he had discovered:

"I, by the leave of so great men, would say that not any of them by a particular inquest have searched the Lurkings of these Lacteal Veins within the Thorax. But I believe this is rather to be attributed to their misfortune than negligence, because none of them knew that the Chyle was not derived to the Liver, nor to the *Vena porta,* nor to the *Vena cava* near the Emulgents, as the received errour held forth: but, which in dissection may be seen to any man more clear than the light, *From the Guts to a certain* RECEPTACLE of that bigness, which will fill up the *interstitium* between the *Lumbar Muscles,* at least in Beasts.

"Now this receptacle above the Vertebers of the Loyns receives the Liquor of the Milkie Veins spread in the Mesentery, and rendreth it again by those Milkie Veins, which being hid within the breast, in a continued passage run to the Subclavial venal branches, till within the ascending stem of the *Vena cava* about the External Jugulars, being mixt with the

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[3] Comments and translation from Professor Edward K. Rand, Harvard University: "The elegaic couplet in honor of Gaspar Asellius indeed presents a little problem. There probably is a question mark after GALENI. I should not expect the question mark, but there it is, and it gives the same meaning anyway. The *haec* ought to mean 'the latter,' referring to the subject adjacent, i.e., *dextra,* whereas the *illa* would refer to GASPARIS. *Cultior,* I think, does not mean 'more inspired.' It would apparently refer to Galen's fame—i.e., *a pluribus hominibus cultus.* That, however, makes the *dextra* the special property of Galen, whereas it really belongs to Gaspar. However, Galen really did have a right hand of his own after all, so once more, no harm is done. The last line, therefore, I think might be translated: 'that [i.e., the right hand of Galen] has more renown; his [i.e., Gaspar's] was not less sure'."

blood, and running in one and the same Chanel, it throws its self headlong into the Whirlpool of the *Heart, . . . .*"

Pecquet thus added the receptaculum chyli and the thoracic duct to

FIG. 17.—The thoracic duct and receptaculum chyli of the dog, *1*, and the manner of their exposure, *2*. *H* represents parts of the diaphragm. The numerous large cross connections and the large right duct are overdone; but the right duct in the dog is often large and heavily loaded with chyle, so that the drawing, though extreme, is not beyond the facts in certain cases. (From Pecquet, 1653 translation, Figs. 1 and 2, opposite p. 38. See footnote 4, p. 55.)

lymphatic architecture; and I cannot omit a little of his description of the reason why he succeeded and of the way in which it was done:

"After I had some years ago, by Cutting up of Dead Bodies, acquir'd a dumb (I may say) and cold Knowledge, I resolved to squeez forth true knowledge from the Harmonie yea of twenty Living Creatures. And be-

cause these differ from the former almost onely in Motion, which hath its chief seat in the Heart, It was my purpose, having uncloathed and cut out the Heart, to contemplate it more manifestly.

"Therefore having cloven asunder the Thorax of a Great Hound, I begun my view of the contained parts without delay; I pluckt out the Heart, having cut asunder those Vessels wherewith it was tied to the rest of the body; The abundance of blood, which immediately flow'd, did at present stop my prying sight; that being spent, I did wonder to see flowing in the Pipe of the *Vena cava* at its connection to the right Ventricle a milkie liquor, casting it self out by intermission."[4]

At the time when Jean Pecquet—in the practice of his preaching—took that unfortunate overdose of his cure-all, brandy, interest in the lymphatics was shifting northward. Rudbeck, a brilliant observer, and Thomas Bartholin, the first to use the term "lymphatics," and others (Fulton, 1938) pushed on the gross anatomy of the lymphatics until, by 1700, it was well known that in man and many of the larger mammals there was this system of vessels, separate from the arteries, which came from many different parts of the body, and that eventually the fluid which these vessels contained reached the blood through the thoracic or the right lymphatic duct.

In the two preceding lectures I have returned again and again to the fundamental place of the lymphatics as part of a larger circulatory arrangement, and have said little of the most easily traced feature of the system, the lacteal vessels and their relation, through the intestinal villi, to fat absorption. It was the lacteals with their conspicuous, creamy content that brought about discovery of the lymphatics. There are many still who, seeing or hearing of this very definite physiological performance relative to fat, think of it as the sole task of the lymphatics, neglecting the more general and important duties of these vessels in so far as we know them. It is certain that the lymphatics of the small intestine in mammals have become specialized for fat absorption, but whether 60 per cent or wholly responsible for this vital part of nutrition cannot be said, since the methods so far used to examine the problem have not been controlled either by knowledge or by regard for the possible ways in which intestinal lymph may reach the blood.

When the Hunters came upon the scene (William, 1718–1783, and John, 1728–1793), the problem of the mammalian lymphatics had become

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[4] From *New Anatomical Experiments of John Pecquet,* pp. 4–8. Printed by T. W. for Octavian Pulleyn, London, 1653. This translation of Pecquet's *Experimenta Nova Anatomica,* 1651, is extremely rare, there being, so far as can be learned, about six copies in existence. Our own efforts and those of James Ballard of the Boston Medical Library being unavailing in discovering the name of the translator, Dr. John F. Fulton was kind enough to explore the problem, but reports no success.

largely histological and physiological; but the methods of study pursued were still those of gross anatomy. While the reasoning was toward function, it was reasoning, not direct experiment. William Hunter regarded the lymphatics as his private property—a state of mind which medical investigators have often assumed toward the children of their intellects, and which no doubt they will display as long as man is man and so cherishes his unhappy store of self-consciousness and vanity. William had the merit of recognizing that the great system of lymphatic vessels, which he knew went far beyond the lacteals, must have some general task, as contrasted with the blood vessels. These latter were obviously for distribution of necessary substances, while the lymphatics accomplished absorption, a fact quite evident in connection with the intestines but equally true elsewhere. In 1784, in lectures published after his death, his statement of lymphatic function is much to the point, and leaves no doubt that William Hunter and the answer to the problem of lymphatics are as indissociable as California and sunshine, or other unassailable factual association:

"I think I have proved, that the lymphatic vessels are the absorbing vessels, all over the body; that they are the same as the lacteals; and that these altogether, with the thoracic duct, constitute one great and general system, dispersed through the whole body for absorption; that this system *only* does absorb, and not the veins; that it serves to take up, and convey, whatever is to make, or to be mixed with the blood, from the skin, from the intestinal canal, and from all the internal cavities or surfaces whatever. This discovery gains credit daily, both at home and abroad, to such a degree that I believe we may now say, that it is almost universally adopted: and, if we mistake not, in a proper time, it will be allowed to be the greatest discovery, both in physiology and pathology, that Anatomy has suggested, since the discovery of the circulation."[5]

The two Hunters were of enormous importance to medicine, but one cannot feel a loss in not having been intimate with them. Their findings, their beliefs were too certain for endurance—invariably the case with persons who are always right. There was one redeeming feature prominent in both brothers. They were fighters, but they turned to experiment for their ammunition. When they could, their arguments were charged with new explosives, not the remade old statements which were expected by their many adversaries.

It is not surprising that William Hunter, being perfectly sure that the lacteals carried absorbed material, should extend the idea to lymphatics from other regions and should develop a generalization that the lymphatic

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[5] From William Hunter's *Two Introductory Lectures to His Last Course of Anatomical Lectures at His Theatre in Windmill St.*, pp. 58–59. J. Johnson, London, 1784.

FIG. 18.—A figure illustrating how thoroughly the gross anatomy of the human lymphatic system was understood by the end of the eighteenth century. (From Cruikshank, 1790, Plate 1, preceding p. 209. See footnote 6, opposite.)

system was the great absorbing mechanism. This said, he was at once confronted with assertions that many animals which, to live, must certainly absorb from the intestinal tract apparently had no lymphatics. These assertions referred to the failure to find lacteals in fish, amphibians, birds, and reptiles. It did not take long to meet this contention.

" 'Accordingly, my brother, Mr. John Hunter, whom I bred to practical anatomy, . . . . found some lymphatics, first in birds, and then in a crocodile.

" 'Next, Mr. Hewson, whom I bred to anatomy, . . . . discovered . . . . the lymphatics and lacteals, both in birds and fishes; . . . .

" 'And, last of all, Mr. Cruikshank, whom I likewise bred to anatomy, . . . . has traced . . . . that system in almost every part of the body . . . .' "[6]

How thoroughly the work was done is apparent in Figure 18, which is Plate 1 from Cruikshank's work and shows clearly enough the gross distribution of the human lymphatic system. More significant, but somewhat less spectacular, were the labors of the second of William's anatomical offspring, the engaging but pugnacious Mr. Hewson, who, with his foster brethen, not only dissected the lymphatics of man but made thorough examinations in fish, turtles, and birds. Hewson, about 1763, described the mesenteric lymphatics in a number of different vertebrates—turtles, birds, and fish—finding first the vessels in the mesentery, then the receptaculum, and eventually the right and left ducts with their terminations in the veins. His descriptions of the system, which appeared in detail in 1774, are quite astonishing. First of all, the size of the lacteals was small. They contained a clear, not a milky, fluid, and there were no mesenteric lymph nodes to guide him to vessels. In the case of fish, his summary left little for the future; but his findings have often been rediscovered and printed.

In fish, the lacteals and lymphatics "are remarkable in not having any lymphatic glands. . . . . In this they agree with the turtle, but differ from birds, which have lymphatic glands on the vessels of their necks." Curiously enough, these first nodes are found only in certain diving birds, and the wide distribution to which we are accustomed is not found, except in the mammals, and then in greatest profusion in man. If valves are present in fish lymphatics, Hewson observed, they are so rudimentary as readily to permit retrograde injections which fill an elaborate meshwork of vessels "between the muscular and the internal coat." This network he related to the villi described in man by Lieberkühn in 1745. The villi enormously

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[6] From William Cruikshank's introduction to his *Anatomy of the Absorbing Vessels of the Human Body,* p. 5. G. Nichol, London, 1786. Also pp. iv and v, 2d ed., 1790.

increase the absorbing surface of the intestine. They are contractile structures, well supplied with blood capillaries, and in the center there is a large lymphatic which, when fat is being absorbed, is filled with the creamy fluid so easily collected from the lacteals in the mesentery. When an animal is deprived of fat, the lacteal lymph is clear and relatively rich in protein. Contrary to the belief of many, it flows freely in the absence of fat—an independent free flow which I believe important, since without it the addition of a quantity of highly concentrated emulsified fat might readily make a hard task of the movement of chyle.

Hewson, in 1774, realized the structural differences in the arrangements of the intestinal lymphatics of fish and mammals but did not know that the milky fluid, which marked the lacteals of dogs so prominently, owed its whiteness to fat, and that this fact probably expressed the development of a surprising specialization in lymphatic function. The surface of the intestinal mucous membrane varies among mammals, and even more so as one passes down the scale of vertebrates and compares different animals. Bujard (1909), in a variety of mammals and birds, studied the ways in which the mucosa projects or is folded in ridges, the result being increased surface for absorption. The arrangement found seemed to depend upon such factors as the diet and the length of the intestine. Figure 19, *A*, shows

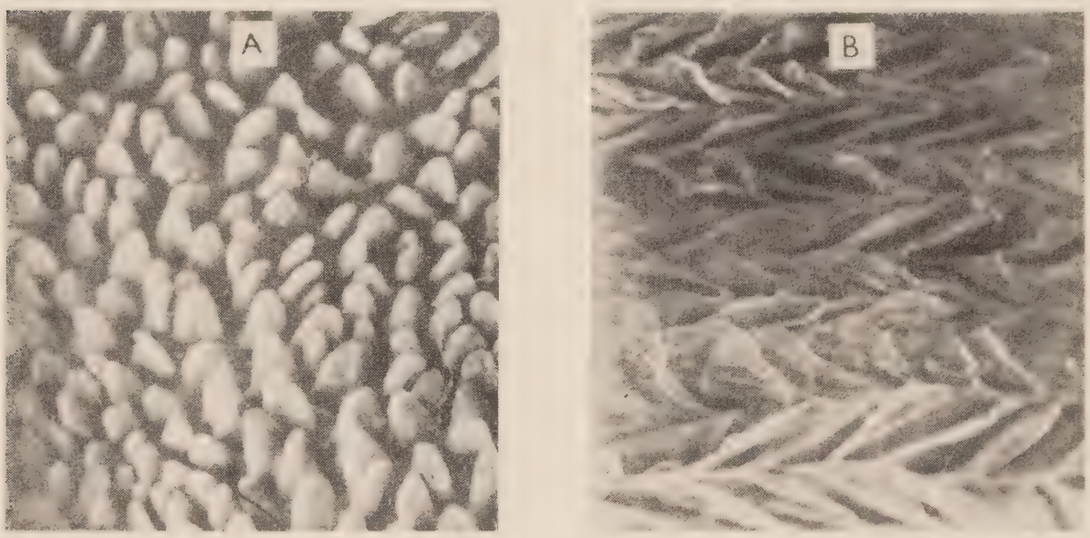


FIG. 19.—*A*, the surface of the upper part of the small intestine in a young white rat. Typical villi are evident. *B*, a lamellar type of intestinal surface from a roughly similar part of the small intestine of a starling. (From Bujard, 1909, Plate 8, Fig. 37; and Plate 9, Fig. 41.)

a villous surface from the upper part of the small intestine of an omnivore, a young white rat. *B* is another type of surface from a similar region in a seed-and-fruit eater, a starling.

The comparative histology of the intestinal mucosa has had much attention, but unfortunately this has not been accompanied by considerations of physiology, particularly in relation to fat absorption. Apparently the intestine of all vertebrates is heavily supplied with lymph capillaries. I have mentioned the lymphatic network in the mucosa of fish, described by Hewson (1774). Langer (1866) injected the intestinal lymphatics of frogs. Figure 20, *A*, shows adjacent folds of upper intestinal mucosa containing an extensive lymphatic meshwork and declared by Langer to be free of escaped injection mass. *B* is a cross section of similar material; and evidently the lymphatic capillaries are concentrated in the center of the narrow folds which serve as villi but are not histologically similar to those in man or the carnivorous mammals, where each villus contains a large central lymphatic connected with a diffuse net in the substance of the mucosa.

These few illustrations convince one of differences in the lymphatic supply of the intestinal mucosa, but unhappily there are but few data on the composition of the lymph from the lower vertebrates and no information, such as might readily be obtained, on the fat content of their chyle. There is an old and unsettled battle as to whether all the fat absorbed by man is via the lacteal route or whether some of it enters the blood. In the case of fish, it has been asserted that the lymphatics in the submucosa of the stomach contain fat droplets, if fat feeding has preceded death, and that these are absent in starved specimens (Van Herwerden, 1908). This is a finding pointing toward lymphatic absorption of fat, even in fish, but is not accompanied by evidence as to the blood, the food, etc.

It is nothing more than a guess based upon such evidence as I have found, but it seems to me probable that if fish, amphibians, reptiles, and birds are fed with fat, and then blood and chyle collected—care having been taken to see that chyle does not enter the blood—it will be found that in fish, where the intestine is short and relatively simple, fat will be taken up freely by the blood; and that this arrangement—traced through amphibians, reptiles, and birds—will slowly give way to dominance of lymphatic absorption as the experiments are extended to mammals. If such be the case, it will not be surprising to find mammals that retain an abnormal degree of fat absorption by the blood; and, in animals with typical contractile villi, it may well be that in the lower ileum, where villi are not so numerous, fat which is unabsorbed higher up is taken in through the blood.

No one knows how fat reaches the lymphatic in the center of a villus. The arrangement and structure of the villi and their prominent relation to fat absorption make them a specialized part of the lymphatic system. In experiments in my laboratory, fat from chyle collected from the thoracic duct of dogs and given intravenously to dogs, passed slowly out of the

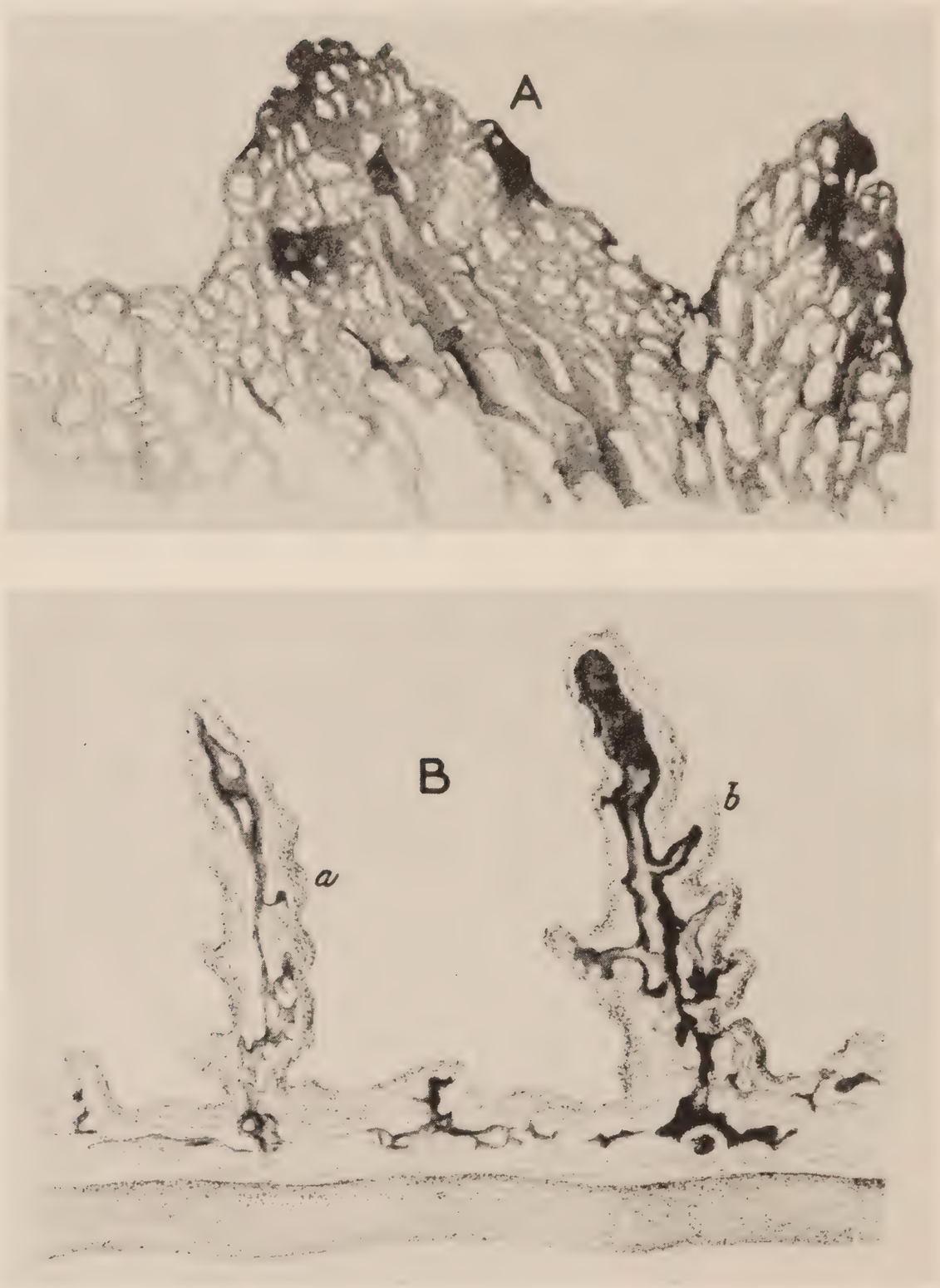


FIG. 20.—*A*, the lymphatic network in a fold of mucous membrane from the beginning of the intestine in a frog, *R. temporaria; B*, cross sections of similar folds showing the central position of the lymphatics. (From Langer, 1866, Plate 1, Figs. 6 and 10, following p. 422.)

blood capillaries and was found in small amounts in cervical lymph. This means that fully formed fat traverses the endothelium of capillary lymphatics in the skin, mucous membranes, and other possible tissues drained by the cervical lymphatics. Such being the case, fat reaching the walls of lymphatic capillaries in the bowel—whether the vessels are diffuse nets as in the frog or the contractile villi of mammals—enters the lymph stream. But when one is familiar with the viscous, creamy lymph which may be collected from the lacteals of a dog after a heavy meal of fat, it would seem reasonable that a propulsive and diluting mechanism, such as the villus, is almost essential for handling the task of getting the fat to the blood for general distribution. All the vertebrates eat fat, but mammals and paricularly man often ingest pure fat in large amounts and require absorption on a large and rapid scale. Birds, fish, reptiles, and amphibians are seldom in a position to obtain a large amount of fat. To absorb what is present in their food, they must slowly break it out of masses of cellulose, protein, etc.; so the problem of dealing abruptly with a large amount of relatively pure fat does not confront them, and a special mechanism for the task of absorption is perhaps not essential. It will be remembered that fish lymphatics are without valves, and that valves are insignificant or absent until mammals are reached; so that lymph movement is but casual in such vessels as the lacteals of fish, and, given a heavy load of emulsified fat, lymph flow would be very slow.

Whatever the answer to the problem of fat absorption, it is within experimental reach, since even in animals as small as the usual laboratory frog it is now possible to collect lymph and blood during periods of fat deprivation and periods of fat feeding and so not only to settle an old problem for mammals but also, perhaps, through gradual steps to illustrate the development of one of the most specialized features of the lymphatic system.

It was long after Hewson before modern histologists and embryologists really began to understand something about the ordinary lymph capillaries distributed throughout the body, not merely those assigned to special duties in the villi. The first step, just as had been the case with the blood capillaries, was to learn the actual structure of the smallest lymphatics and so cease to depend upon theory and argument as to how lymph was formed. It will be recollected that Hoyer, through silver impregnation, outlined the endothelial cells of the blood capillaries in 1865; and it happened that von Recklinghausen, in 1862, showed that the lymph capillaries, similarly treated, displayed the same outlines of plate-like endothelial cells. This demonstration established the cellular structure of the finest lymphatics but by no means settled a controversy that had continued with gratifying acrimony since before the time of William Hunter and his Hunterian broadsides, and

which left the lymph capillaries little place in the sun except as the final elements in an absorbing system.

But taking absorption as a settled fact did not satisfy anyone, except perhaps William Hunter and his anatomical progeny. The problem simply moved on another step and became centered upon the way in which the lymph capillaries—inert structures with no obvious inherent power to collect fluid or anything else—contrived their absorbing. Was it secretion? Were there holes in the lymphatics, which made their interior continuous with the tissue spaces? Sabin (1913) has provided four diagrams which reach back before the Hunters and bring the structural issue, i.e., integrity of wall, to its present position. The steady and conclusive advance of knowledge, particularly the advance from the idea of lymph capillaries opening freely into tissues to that of closed vessels, was not easy for physiologists and pathologists to swallow. The trouble was that almost anything—foreign particles larger than red cells, blood proteins, an infinity of substances, many of them on the large side of what are called "microscopic particles"—when placed in the tissues, and without the possibility of trauma's causing entrance into lymphatics, somehow or other reached the current of lymph and, eventually, if very large and very insoluble, came to rest in a lymph node. There were many who believed that this freedom of entrance into lymphatics must depend upon some sort of sieve-like structure of the endothelium; but this is not the case. The typical lymph capillary, as found in the skin, is a vessel with unbroken walls, which are freely permeable to water and to normal blood solutes that have passed through the walls of the blood capillaries and have entered the tissue fluid. Under the influence of motion, massage, or increase in tissue pressure—such as accompanies swelling—serum albumin, serum globulin, and foreign substances of microscopic dimensions cross the tenuous wall of the lymph capillary with the greatest ease. Once inside, there is no reason why return to the tissue spaces cannot occur, and it may. At the same time, the situation of a particle within a lymphatic favors drift along the vessel, as a result of the same external pressure or motion which caused lymphatic entrance. When valved lymphatics are reached, the lymph flows to a node and finally to the blood. William Hunter was right in his idea of the lymphatics as "absorbent vessels," but it is an absorption forced from outside the lymphatics and wholly independent of active participation of the endothelium of the "absorbents."

There is a final point relative to the lymphatics which is most important for medicine and surgery, and which is out of accord with conceptions easily carried over to the lymphatics from observation of the more readily traced blood capillaries. The ultimate lymphatics, with endothelial walls so thin it is no wonder they escaped detection over many years, do not run unbranched

for even the slight distances often seen in blood capillaries. The lymphatic capillaries exist as meshworks or as sprouts from nets of vessels wider than blood capillaries. In the case of the skin, man is enclosed in a continuous

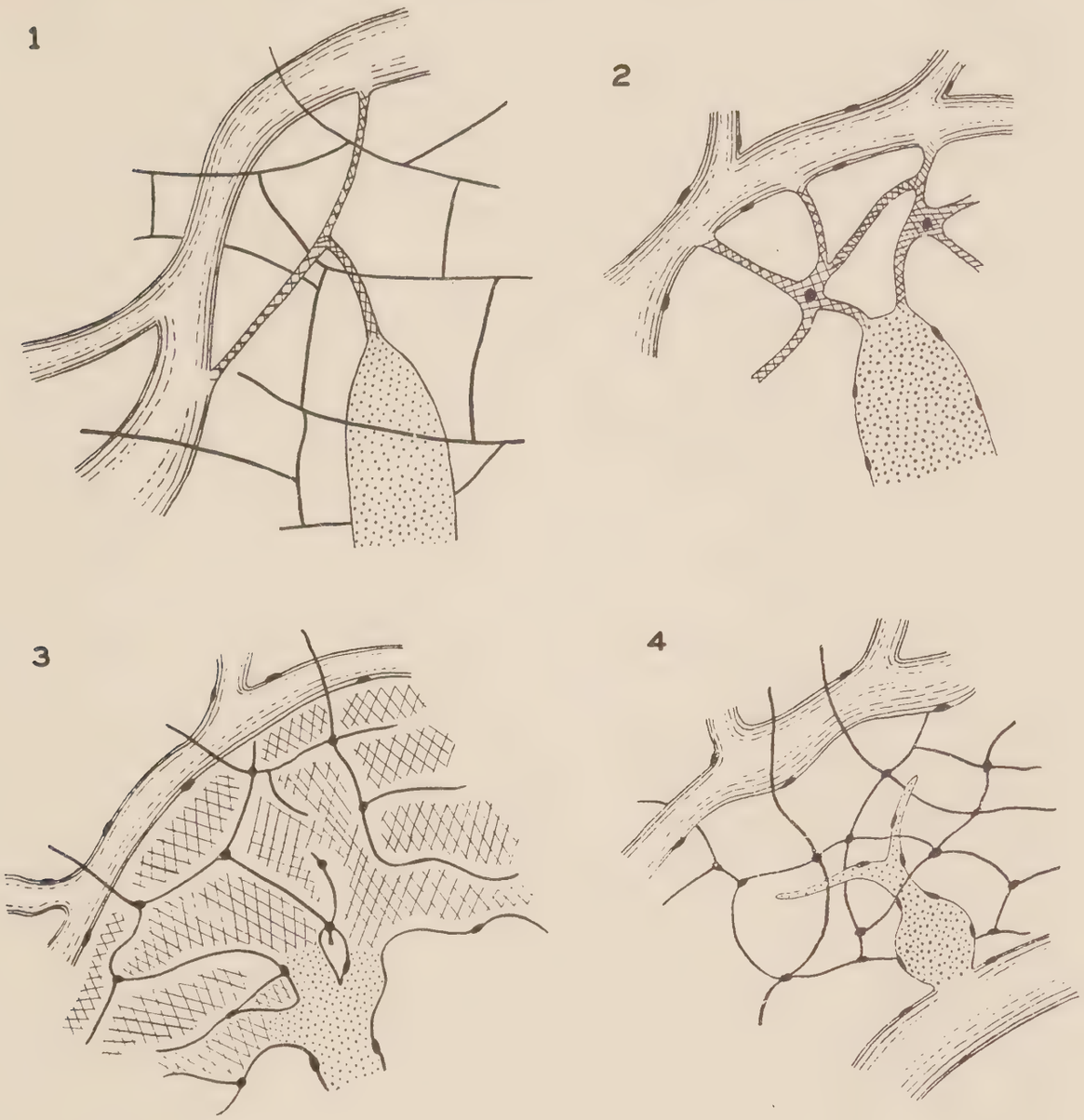


FIG. 21.—*1*, the first effort to explain the origin of lymph and the absence of red cells in lymph by postulating narrow connections between lymphatics, dotted, and large veins. *2*, another version. The lymphatic, dotted, is now conceived to be connected with the vein by narrow tubes of hollowed-out connective tissue cells. *3*, von Recklinghausen's view of the direct communication of lymphatics with the tissue spaces. Lymphatic, dotted; tissues, cross-hatched; vein, along top of diagram. *4*, the modern view. Capillary lymphatic, dotted, a structure with continuous walls and no venous connection. Vein at top of diagram. Dotted lymph capillary enters a large lymphatic at bottom of diagram. (From Sabin, 1913, Figs. 1, 2, 3, and 8, pp. 5, 6, and 33.)

fine-meshed net of lymph capillaries, here and there connected with valved collecting trunks, which compel a unidirectional flow once they are entered. In the lymph capillary net, fluid may drift in many directions, depending upon external influences. Only when the system is full and continuous rapid increments of lymph are being added, as is the case in an area of acute inflammation, is there steady flow toward the veins. In normal tissues no such extravagant filling of the lymph capillary reservoir occurs; and, since the skin lymphatics have a possible capacity as great or greater than the blood capillaries, lymph formation has little effect upon the promiscuous drift of lymph in the network of lymph capillaries, which are more than able to contain all the fluid absorbed.

The free communication between lymphatic capillaries is a characteristic which extends to the collecting trunks. These larger vessels are frequently interconnected through short anastomotic branches. This great degree of communication has much to do with the difficulty experienced in causing lymphatic blockage and lymphedema in the laboratory—an experimental puzzle which extends back to Cohnheim, and which is solved only by continued attacks upon the possible drainage routes, a process simulating that of the chronic diseases most often the cause of lymphedema in man.

There is a second point in relation to lymphatic obstruction, which was shown beautifully by Reichert (1926), in Halstead's laboratory at the Johns Hopkins Medical School. It is the remarkable ability of lymphatics to regenerate. Reichert severed skin, muscles, all save the blood supply and sciatic nerve in the thigh of the dog, his idea being that this would divide all lymphatics, as it surely did. He then sewed the tissues together, and edema appeared fairly promptly; but he also showed, by means of injections, that new lymphatic channels began to cross the wound on the fourth day following operation, and by the eighth or ninth day the lymphedema was gone!

This intense power of regeneration after trauma or during the destructive attacks of disease argues that the lymphatic system, which appears so suddenly in fish, has not only gained an astonishing structural complexity and wide distribution in the mammal but at the same time has become an indispensable factor in the accomplishments of the total circulation. While at times the lymphatics play an evil part, their normal functions must be vital to the steady operation of the complicated mechanisms which maintain in the tissues the relatively unchanging conditions necessary for life and health.

# IV. BLOOD, TISSUE FLUID, AND LYMPH AS ILLUSTRATED BY EXPERIMENTS UPON THE HEART AND LUNGS


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In the preceding lecture the gradual understanding of the structure of the widespread networks of lymph capillaries was described, and it was emphasized that these almost invisible vessels possess a continuous lining of endothelium and are not open to the tissues.

The modern physiology of the lymphatic system received its first great impetus from Carl Ludwig and his pupils a little after the middle of the last century. Their direct attack upon what had been almost wholly speculation was one of the many contributions from that extraordinary focus of physiological experiment, the Leipzig laboratory. Ludwig, with characteristic clarity of view, wasted no time on conceptions of lymph flow and composition derived from theory. Moreover, he was too wise to depend upon experiments in which the thoracic duct was cannulated and a mixture of lymph obtained that came from too many sources to be related to any special group of blood vessels. Very soon Ludwig's pupils began to collect lymph from such minute lymphatics as those just above the foot in the dog, and from other regions where lymph was related more directly to filtration from the blood than was chyle or lymph from the thoracic duct. Dogs, usually heavily narcotized with opium, were the animals of choice; and there resulted a clear demonstration of the effects of massage and of active and passive motion in causing lymph flow. Ludwig became convinced that lymph was a filtrate from blood, and certainly not a secretion derived from the tissue fluid. I cannot give time to the numerous papers which supported this belief. They did not establish Ludwig's own conviction of filtration, since he lacked chemical methods for adequate analyses of the small amounts of lymph collected; but, as time has passed,

there is no doubt that the filtration theory of lymph formation is another of the many instances of sagacious and correct insight so typical of Carl Ludwig.

About ten years after Ludwig's day, Rudolph Heidenhain, in Breslau, again advocated the idea that lymph was secreted, the raw materials being taken from the tissue fluid. The trials of the medical student in physiology even to the present time have involved, with other evils, the necessity of memorizing a long series of substances—some as obscure as leech extract—which Heidenhain listed as lymphogogues. Not only did he afflict medicine with a list of these substances, but, with characteristic Teutonic industry, he separated them into various classes. To distinguish and remember these was a further torment to the medical student, and of no use to anyone.

Happily, Heidenhain had a pupil, Ernest Starling, who entered the lymph problem as zealously as he explored other fields in physiology during his productive life. After a time the young Englishman, having wrought in Heidenhain's mold, returned to England and began to think for himself, with results which soon carried him back to the older and more brilliant German, Ludwig.

The modern history of lymph formation and lymph movement began with Starling. In 1893, he wrote on the physiology of lymph secretion. A year later, there was a paper upon the influence of mechanical factors on lymph production; and so on, until, as shown diagrammatically in the first lecture, the mechanism of exchange between capillaries and lymph took modern shape. Those who have reworked the field, though able to describe many things which would have been immensely interesting and gratifying to Starling, have added comparatively little to the fundamental principles which he formulated of lymph formation and of the movement of fluid from and into blood capillaries. Starling's evidence, though often technically crude, was, nevertheless, the product of an intelligence which had a habit of being right in the great essentials.

Starling reasserted that such general influences as active and passive motion and massage were responsible for lymph flow from most regions. The facts that lymph could be obtained from a leg lymphatic only through some external influence, such as muscular movement, and that in quiescence nothing short of toxic alterations in the blood capillary endothelium produced lymph formation and flow, disposed of the secretory theory of Heidenhain—which, unhappily, has taken the usual number of years to disintegrate commonly required by elaborate mistakes incorporated in medical textbooks and repeated from author to author.

In 1926, with Dr. Churchill, now one of the professors of surgery in the Harvard Medical School and one of a number of surgeons whom, to

paraphrase William Hunter, "I have had the pleasure to breed to physiology," some experiments on frog lymph were undertaken, since it had occurred to me there might be something there which could not be accounted for by the current idea of the almost complete impermeability to the blood proteins of capillaries in the skin of the frog. Since 1926, aided by many associates, I have continued to pursue the hare made to break cover by Starling; and this pursuit, which began first with the hope of converting into usefulness conceptions which had resulted from few experiments, has moved step by step toward quantitative results. I shall not describe the many diversions from the basic plan to examine the normal physiology of the lymphatics and to ascertain the factors determining composition of lymph collected from various parts of the body. From this single purpose we have been turned aside by many questions. Crystalline particles have been followed from the tissues or from the blood capillaries, through the tissues, into the lymph and into the lymph nodes. We have watched the violent activities of the microfilariae, so often found in a serious disease of the dog, as they have passed from the blood into the lymphatics and lymph nodes. These organisms are often as large as the capillaries they leave, and are a tight fit for the lymphatics they enter. We have compared lymph flow and lymph pressure from areas of acute inflammation with flow and pressure from comparable areas which were wholly normal (Field, Drinker, and White, 1932). We have attempted without success to trace viruses, such as that of poliomyelitis, from the mucous surfaces of the nasopharynx into subjacent lymph capillaries, and eventually into the lymph collected from large draining vessels. These and many other practical issues—invariably hard to resist by one whose early days were spent in the medical clinic—have diverted, but never extinguished, interest in the basic problems of the normal physiology of lymph production and lymph movment; and in the relation of the composition of lymph, collected from region after region and organ after organ, to the composition of blood capillary filtrate and tissue fluid.

In order to learn the normal performance of any organ or system, the physiologist must first devise experiments in which the condition of the tissues studied is normal or, if abnormal, is susceptible of the repeated reproduction essential for conclusive observations. Experience with the collection of lymph from vessels running beneath the skin in the leg of the dog, and from the cervical collecting trunks, showed that lymph could easily be obtained by manual massage in amounts sufficient for qualitative determinations of composition and volume of flow. At the same time, lymph flow due to massage was variable; and this simple method of obtaining lymph soon demonstrated that one of the first requisites for real knowledge was the finding of a method which would impose constant

conditions of lymph formation and lymph movement upon a definite area of tissue.

Our first approach to such a preparation was the repetition of an experiment by Emminghaus (1873) in Ludwig's laboratory. Emminghaus cannulated lymphatics at the level of the wrist or ankle joint in dogs narcotized with opium. Under local anesthesia, we found it easy to cannulate the same lymphatics, the cannula being secured in place by a stay suture. Fairly constant conditions of lymph flow and composition were then maintained by causing the dog to walk or run for definite periods of time. The lymph collected was a third or perhaps a half of that from the foot and the tissue a little above it—too small a region to give satisfactory quantities of material for complete analyses, unless the experiment was very long. It was difficult to maintain a steady flow of lymph over protracted periods because, after a while, the dog—no matter how much a pet of the laboratory staff—bored with walking, insisted on either sitting or lying down. This does not mean that valuable information did not emanate from many experiments done in this manner, both by ourselves and by others. But the practical difficulties of the method made us dissatisfied with it as a source of quantitative data.

Following this effort, a fruitless year was spent in trying to induce uniform lymph flow by mechanical massage of the hind leg. Lymph was collected from a large vessel in the thigh of a dog under nembutal anesthesia. Massage was accomplished by rhythmic compression of the limb with a column of mercury caused to rise and fall in a brass tube in which the lower leg of the dog was inserted, a rubber sleeve being interposed between the mercury and the skin of the animal. The repeated compression and release of pressure, provided by the rise and fall of the mercury, promised at first to be a very efficient means of uniform massage. As time passed, the ingenuity and mechanical perfection of the apparatus slowly took entire charge of the experiment. Lymph flow and composition, however, displayed a discouraging variability, especially mortifying in view of the pleasure one had in contemplating the operation of the mechanical massager, provided it was not being used in a physiological experiment but was merely being demonstrated to friends as a promising way to attack an old problem. As is the case with so many experiments which ought to work, but do not, it required many months to consign the increasingly complicated apparatus devised for this effort to a secluded region in the basement, and then to start anew.

The experiment devised next depended upon mechanical arrangements which were extremely simple. The results as to normal composition and flow of lymph, and the modification of these findings by such common experiences as lowered blood oxygen were quite satisfactory. Very briefly,

in a dog under nembutal anesthesia, the right and left cervical lymphatics were cannulated so as to collect their delivery of head lymph. The animal lay upon his back. Tapes fastened around the tip of the snout were connected with a motor-operated crank, which, as it revolved, caused the head to extend upon the neck. When the extensor pull was released, rubber bands—also fastened to the snout—flexed the head, so that there was a slow but constant nodding, which could not vary in the slightest degree over many hours (McCarrell, 1939). The results have been described at length, and the method has had ample trial.

An experiment of this sort, in which there is repetitive passive motion of a part, is still to a degree unsatisfactory, being unaccompanied by any functional activity of the tissues in the region from which lymph is collected. Furthermore, one cannot be sure the lymph obtained in different experiments comes in constant amounts from the different tissues in the area drained.

Another trial was made. This time a lead from California was followed—a lead obtained from a paper by Patek (1939) on the anatomy of the lymphatics of the mammalian heart. After a short search in the anesthetized dog, a large lymphatic was found between the superior vena cava and the innominate artery. This proved extremely constant and was found, as a result of many injections, to carry all the lymph from the beating heart. To cannulate this vessel it was necessary to employ artificial respiration and to expose the anterior mediastinum by removal of the sternum down to the base of the heart. The entire chest was not opened by this exposure, and the conditions of the experiment were as good as those which attend most direct explorations of cardiac function in mammals. Using this preparation, it was found first of all that the lymph flow from the heart was exceedingly constant unless cardiac activity was disturbed, a fact well shown in Figure 22. Subsequent experiments showed conclusively that when the work of the heart was increased by the use of adrenin or ephedrin or, in a Starling heart preparation, by increased cardiac inflow and output, the flow of lymph rose immediately, and fell when the work was reduced to normal (Drinker *et al.,* 1940). Later, Maurer (1940–1941) showed that if the blood oxygen was decreased so as to reach a saturation of 75 per cent, lymph production increased and became very great when the blood was about half-saturated, which would be the case if the animal were at an altitude of 20,000 feet and breathing air.

The lymph supply of the heart is a matter which has escaped serious medical consideration and should certainly be studied by injection methods in diseased hearts of varied sorts. Figure 23 shows two sections of muscle from the normal heart, with injected blood and lymph vessels. The lymphatics are black, and the blood capillaries lightly shaded. The extent of

the lymphatic bed is obviously very great. It is not surprising, therefore, that in our experiments the flow of lymph from the heart in healthy dogs was often large—varying from animal to animal, though heart weights were quite similar, but in a satisfactory preparation always surprisingly great. It is of interest that under the influence of low oxygen, just as is the case in other parts of the body, the heart lymph soon began to contain numbers of red cells, indicating a change in the blood capillaries, but one

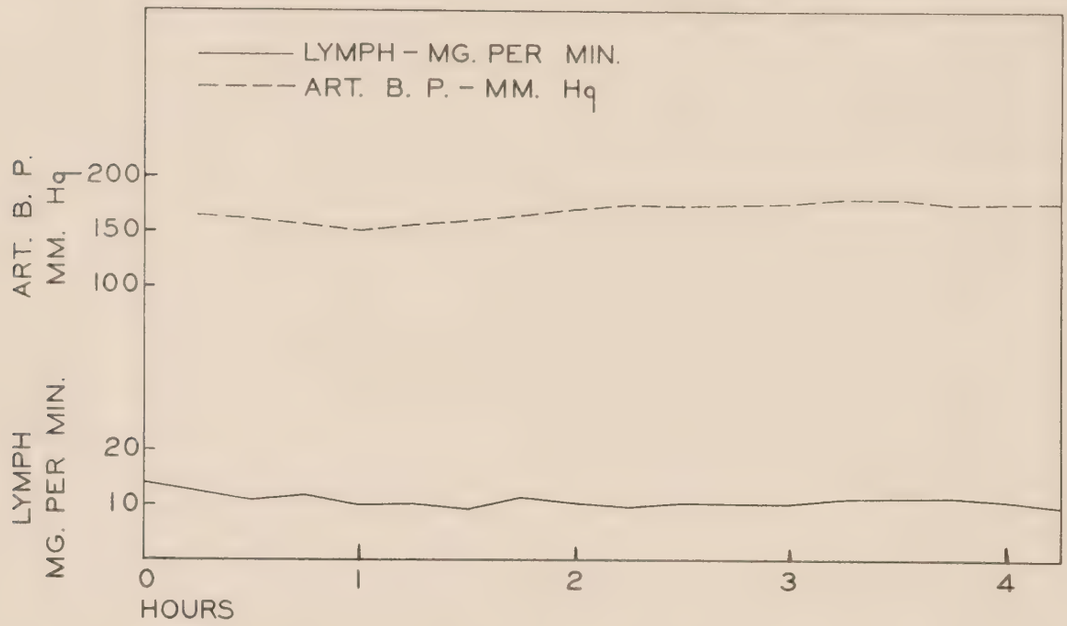


FIG. 22.—The steadiness of normal lymph flow from a dog's heart. *Ordinates: uppper curve,* arterial blood pressure in millimeters of mercury; *lower curve,* milligrams of lymph per minute. *Abscissae,* time in hours. (From Drinker *et al.,* 1940, Fig. 2, p. 44.)

which we have gradually learned is not as serious as it appears to be and not necessarily indicative of a dangerous sort of capillary leakage. Erythrocytes may escape with fair freedom from capillaries, which at the same time do not leak protein in amounts far above that occurring during preceding normal conditions. It is as though the red cells found their way through the endothelial wall of the capillary, acting as plugs against fluid leakage during their period of transit. There is no question that when anoxemia is prolonged and severe, capillary endothelium is damaged, so that free escape of blood proteins occurs. This state of increased permeability may resist return to normal in a very dangerous way, assisting in lowering of blood volume and helping in the production of that unfortunate complexity of dangers called surgical shock.

There are features of the possibilities inherent in the examination of the flow and composition of heart lymph useful in general ways. First,

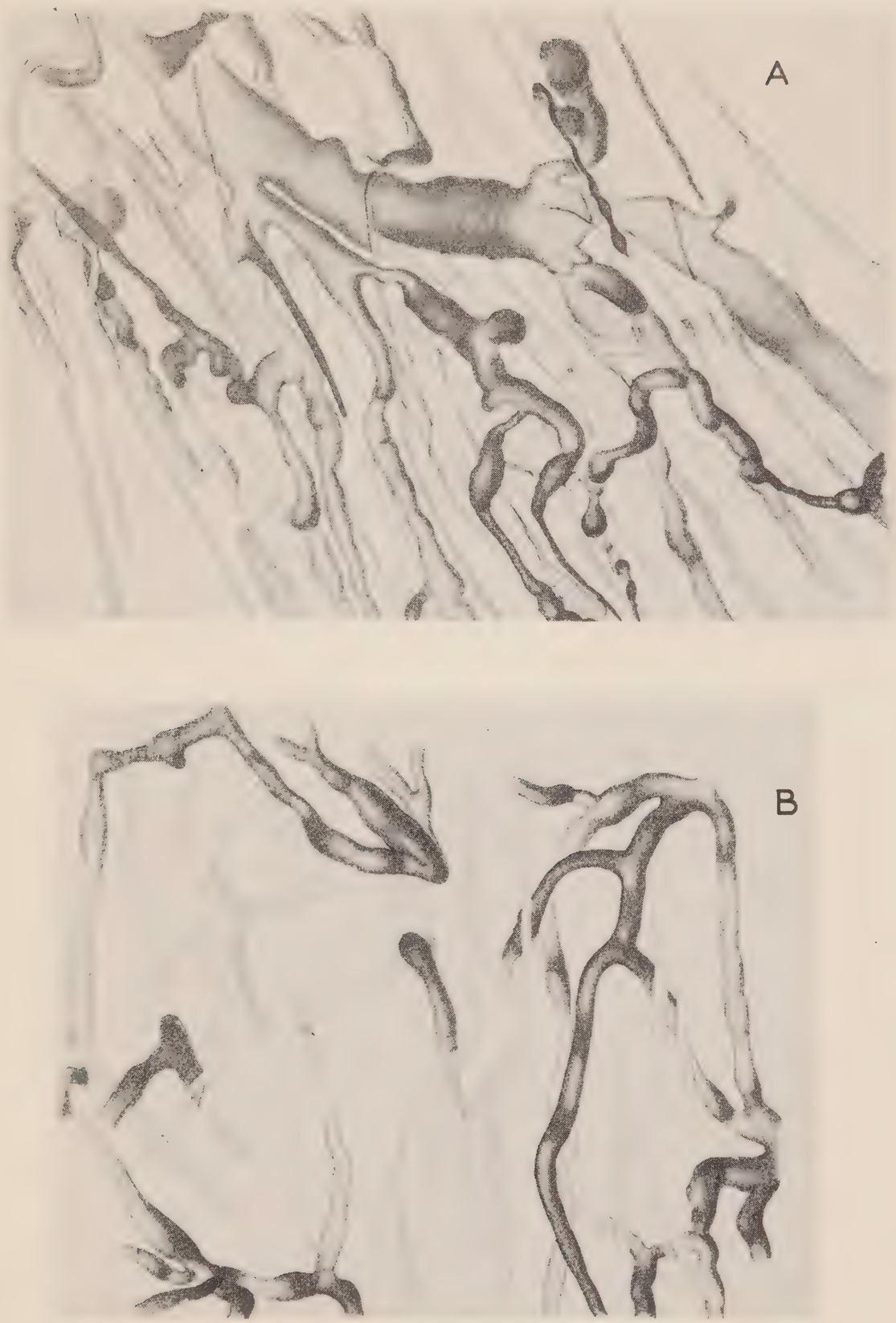


FIG. 23.—Two views of the lymphatics in heart muscle. Lymphatics dark; blood capillaries light. *A* shows a large trunk with smaller connecting vessels, probably from muscle just under the epicardium; *B* shows the situation in the depth of the muscle. (From H. Bock, "Die Lymphgefässe des Herzens," *Anat. Anz.,* 1905, **27,** Plate 2, Figs. 3 and 8, following p. 40.)

one can obtain lymph, which in flow and composition represents the entire output of a single organ, the heart. Second, there is a comparable supply of pericardial fluid, which is a transudate from epicardial vessels. One may compare the results of chemical analyses of these two filtrates from the cardiac blood with the blood itself, since both heart lymph and pericardial fluid are obtainable in amounts large enough for a number of measurements. A few data of this sort are available, data gathered during the brief period in which we have known how to collect this lymph.

A group in my laboratory (Drinker *et al.*, 1940) obtained from six dogs the average values shown in Table I. The figures in this table are

TABLE I

AVERAGE VALUES FOR CERTAIN CONSTITUENTS AND FOR COLLOID OSMOTIC PRESSURE OF SERUM, HEART LYMPH, AND PERICARDIAL FLUID FROM THE DOG*

| BODY FLUID | TOTAL PROTEIN | ALBUMIN | GLOBULIN | ALBUMIN / GLOBULIN | CHLORIDE | COLLOID OSMOTIC PRESSURE IN MM. $H_2O$ | |
|---|---|---|---|---|---|---|---|
| | % | % | % | | *mg./100 cc.* | | *per gram protein* |
| Serum | 5.95 | 2.98 | 2.96 | 1.01 | 415.67 | 233.8 | 38.2 |
| Heart lymph | 3.83 | 2.20 | 1.64 | 1.34 | 450.33 | 174.8 | 43.7 |
| Pericardial fluid | 1.63 | 0.91 | 0.80 | 1.14 | 433.67 | 58.7 | 42.6 |

* Averages obtained from Drinker *et al.*, 1940, Table 2, p. 49.

so clearly related that the conclusion is unescapable that heart lymph and pericardial fluid are filtrates from the blood. The low total concentration of protein in pericardial fluid is possibly due to the fact that in this case filtration is not only through the vascular endothelium but also through a variable thickness of epicardium.

The observations upon heart lymph can thus be related to questions of normal lymph formation and flow from a single organ during work and when work is suddenly increased. To these data, it has been possible to add experiments showing that oxygen lack increases lymph flow from the beating heart, the increase beginning at the level of oxygen saturation of the blood where other changes—such as increase in breathing—most often become recognizable. This effect, essentially an increase in capillary permeability, is not serious, and is at once reversed if the oxygen supply is increased. The first effect of oxygen lack on capillary permeability occurs at about 75 per cent oxygen saturation of the arterial blood. At 50 per cent saturation, if sustained for even a short time, serious and irreversible or slowly reversible changes are found.

I shall not hazard a guess at the position of the cardiac lymphatic system in degenerative and infectious diseases of the heart. Time has not permitted experiments, and the problem is one not for guesswork but for direct examination in animals and at the autopsy table. My purpose is achieved if you have come to realize that the elaborate lymphatic system in the heart is something which can be injected and studied in all sorts of conditions. And may I suggest that the lymphatics in the normal and the diseased aorta are worthy of attention they have not received. Even more interesting and more difficult will be examinations of the lymphatics in arterioles, first, to establish normal structure, and then to compare with these standards the findings in vessels from very old and from arteriosclerotic subjects.

To the experiments upon lymph flow from the heart, another group may be added in order to illustrate a few of the puzzles the lymphatic system presents. The flow and composition of lymph from the lungs have been practically unknown. Several years ago, approaching the root of the lung through a posterolateral incision in the thorax of a dog, Mrs. Warren and I succeeded occasionally in cannulating lung lymphatics. The lymph collected was always very bloody, and eventually we gave up the struggle but not the desire to try again. Later, during the dissections necessary to collect heart lymph, we became convinced that a large near-by vessel came from the lungs (Warren and Drinker, 1942). On careful trial, controlled in many ways, this proved to be the case. In the experiments which I shall describe, the chest of a dog—anesthetized with nembutal and under artificial respiration—was opened by cutting the upper three ribs on each side several centimeters from the sternum, sawing through the latter at the lower margins of the third ribs, and removing this piece of bone, with the attached bits of ribs, so as to expose the anterior mediastinum. Beneath the superior vena cava and close to the right side of the trachea, there is a lymph node, which, fortunately, is very constant. The node is freed and raised until an afferent lymphatic is found, cleaned, and cannulated. No drawings of this vessel and the surrounding structures in the dog have been made, but Figure 24 from Rouvière (1932), a diagram of the lung lymphatics of man, gives an idea of the position of the cannula and the lymph drainage of the lungs in the dog.

Diagrammatically the vessel cannulated is at *X*, above two lymph nodes in man (as shown in Fig. 24) and above a single node in the dog. This vessel receives lymph from all parts of the lungs, with the exception of lymph from the upper part of the left lobe, which follows the left side of the trachea to the thoracic duct. It is easy to demonstrate this fact. The thoracic duct is first cannulated. A second cannula is then placed at *X* in a lung lymphatic. A 2 per cent solution of T-1824 is then introduced by

a catheter into the lower part of the left lobe through the bronchus, and is not permitted to reach other parts of the lungs. The dye appears at once in the cannula on the right, the lung lymphatic and the thoracic duct lymph remaining uncolored. This crossed drainage is a peculiar phenomenon to

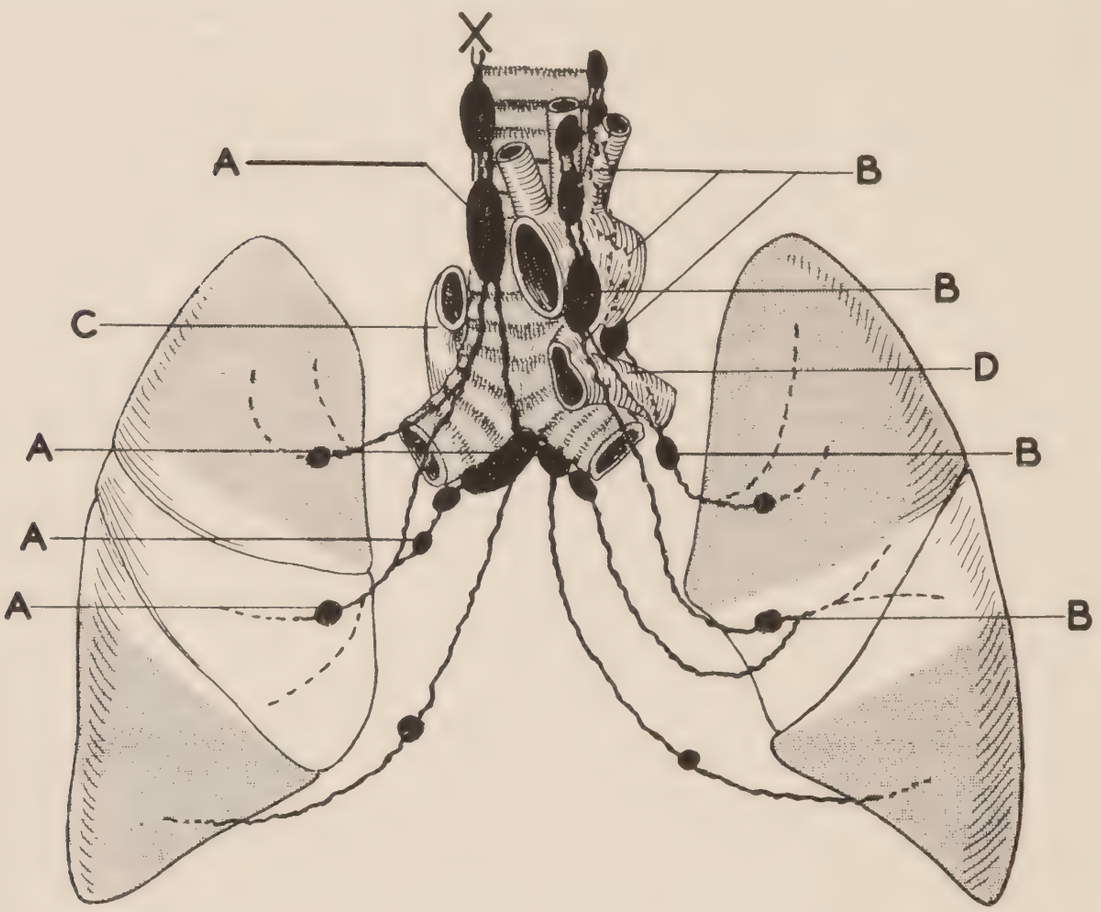


FIG. 24.—Diagram of the lymphatic drainage of the human lungs, which also illustrates drainage in the dog. *A*, lymph nodes on right side; *B*, lymph nodes on left side; *C*, azygos major vein; *D*, pulmonary artery. In the dog the lymphatic is cannulated at *X*, where it emerges from a small node. (From H. Rouvière, *Anatomie des lymphatiques de l'homme*, Fig. 53, p. 217, Masson et Cie, Paris, 1932.)

which, though it has been mentioned many times, little attention has been given. For the purpose of our experiments, it is a piece of the good luck which now and then bobs up in the gamble of experimental work.

The lungs present a puzzling situation when the principles governing the exchange between blood and tissues elsewhere are applied without accompanying experiments. The capillary bed of the lungs is enormous, so much so that the alveoli, encased by a network of capillaries, appear as if inside a cascade of blood, with no spaces between the myriad of interconnected streams flowing over the surface of the air sac. If—as has been

done by Miller—the capillaries in the dog lung are counted for unit areas, with an average capillary diameter of 7μ, one finds that all the available space is filled. This means a maximum provision for gas exchange. It means also a sudden huge increase in the capacity of the pulmonary vessels when the capillaries are reached—a fact which, in its turn, should result in a low capillary blood pressure. To this effect of the large capillary bed in lowering pressure may be added the relatively low pressure in the pulmonary artery. It would seem, consequently—though measurements of pressure in these vessels have not been made—that the pressure in the lung capillaries must be lower than in the systemic capillaries, and that, owing to the elasticity of the lungs and the size of the bed, sudden changes in pressure should not occur. Anyone who measures pulmonary arterial pressure during a variety of conditions designed to cause increase is soon aware of the small gains which accompany great rises in systemic blood pressure. Only when there is obstruction to ventricular entrance of blood, as in compensated mitral stenosis with competent right ventricular muscle, do we find a sustained and material rise of pressure in the pulmonary artery; and with this there should be a higher pressure in the capillaries.

The lungs are apparently safeguarded against undue leakage of water and solutes into the alveolar walls, where edema, with consequent thickening of the tissue, might hinder gas exchange. With this safeguard against capillary leakage there goes the fact that the colloid osmotic pressure of the blood plasma is at normal level and would thus promote absorption of water. That water is freely taken up by the pulmonary blood is easily shown if physiological salt solution is delivered slowly to the alveoli through a bronchial catheter. A fair-sized dog will absorb 1.5 liters an hour without showing ill effects.

These relations of capillary pressure and colloid osmotic pressure are well suited, without other aid, to keep the lung tissue free of excess fluid and to render the alveolar tissue as slight a barrier as possible for respiratory exchange. And yet, in addition to this apparently beautiful arrangement to prevent transudation and to promote absorption by the blood vessels, the lungs are provided with an extraordinarily extensive system of lymphatics (see Fig. 25), and lymph, particularly in man, enters many nodes for filtration before reaching the blood. There is a huge absorbing system in a tissue apparently organized to render such a system unnecessary under usual conditions. The pressure in the lung capillaries is low and, if the walls of the vessels are similar in permeability to typical systemic capillaries, there should be little escape of water and solutes—particularly blood proteins—into the alveolar tissue, to pass eventually into the lymphatics. The permeability of the lung vessels thus becomes a vital factor in the formation of lung lymph.

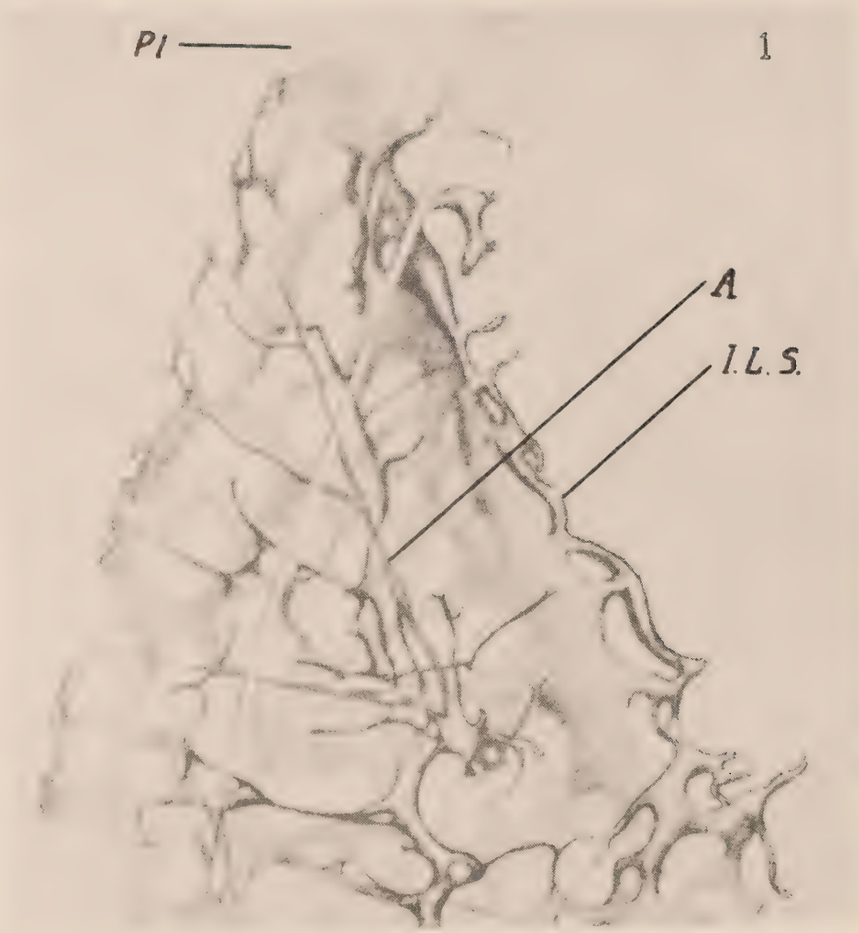

FIG. 25.—The profusion of lymphatics in the lung. *1*, the lymphatics in an interlobular septum, *I.L.S.*, of an embryo pig, injected with Prussian blue, appear as a lightly shaded mesh overlaid by narrow black arterial twigs which have been injected with India ink. *2*, part of the upper lobe of the right lung in an embryo pig. In this case the lymphatic plexus is the dark network of vessels overlying the lightly shaded veins. (From R. S. Cunningham, "On the Development of the Lymphatics of the Lungs in the Embryo Pig," *Contrib. Embryol.*, Carnegie Institution of Washington, 1916, **4**, Plate 3, Fig. 1; and Plate 2, Fig. 4, following p. 68.)

Immediately questions arise. Are the endothelial walls of the alveolar capillaries similar in permeability to those of the skin and of other large areas? If so, are they particularly susceptible to the effects of common experiences, such as oxygen lack, which increase capillary permeability? Does their position in the alveolar walls, which are stretched and relaxed so constantly and in such different degrees, depending upon the extent of the breathing, have any effect upon the endothelial wall? Blood capillaries in the web of the frog are not tubes lying free in the tissue, but are anchored loosely by fine strands of connective tissue, so that upon manipulation they may be sharply bent, and will then return to their original position. The same outside stays have been found for lymph capillaries in the skin, and are one of the reasons why these vessels are held open in edematous parts, rather than squeezed shut as is generally assumed. We know nothing of such possible fixation of the lung capillaries and the obvious implication of distortion and abnormality of the endothelium during heavy breathing.

When fixed and dehydrated sections of normal lung are examined, the alveolar walls are separated by the diameter of the capillaries between them, and the tissue gives the impression of freedom from every vestige of excess fluid. Yet an enormous distribution of lymph capillaries may easily be shown, capillaries extending to the alveolar atrium—that is, to the beginning of the respiratory part of the alveolus. These capillaries are connected with valved vessels which eventually carry the lymph to the root of the lung. I have mentioned the fact that several years ago we collected lymph from this region. It contained just under 3 per cent of protein and many red cells. This meant removal of extravascular protein from the lung tissue; but it did not necessarily indicate that such a process was going on constantly, our operation having been clumsy and traumatizing.

It is clear that if one could collect lung lymph relatively free of red cells (lymph from all parts of the body invariably contains a few of them when examined microscopically), measure the normal rate of flow and the protein content, and then find these altered under conditions which increased pressure in the capillaries or which were known to increase leakage from capillaries in other regions—then one would know that the lung lymphatics function according to the usual pattern, and have not been evolved merely to meet emergencies. No doubt the lymph drainage of the lungs is important in such conditions as pulmonary infections or cardiac decompensation, which require removal of large amounts of more or less proteinized fluid; but it is hard to compass the idea that so elaborate a structural entity as the lymphatic system of the lungs has evolved to serve intermittent needs, potent though they may be.

On the basis of these questions and generalizations, let me now report

what has been learned by direct experiment, the lung lymph being collected from the vessels shown diagrammatically in Figure 24. While these experiments are better than guesswork, our single resource in the past, they have obvious disadvantages. Lymph must be collected during artificial respiration, since it is not yet possible to reach the lung lymphatic in the anterior mediastinum without an open chest. With closed chest and normal breathing, it is conceivable that lymph flow may be even greater than with positive pressure ventilation. Favorable features of the experiment are that the chest opening is so high as to expose only the tips of the upper lobes of the lungs, so that abnormalities due to drying, etc., are avoided and the lungs themselves are never touched in any way.

When the collecting cannula has been inserted and stayed against the right side of the wound by means of a ligature, lymph begins to rise in it; and, as is invariably the case with all lymph collections, clotting and obstruction to flow must be prevented. This is readily done by making a loop, a millimeter or slightly more in diameter, at the end of a fine piece of nichrome or stainless steel wire. The loop is dipped in Ringer's solution and then into dry heparin, which clings to it. By inserting this heparin carrier into the cannula so that the loop reaches the neck, the lymph encounters heparin at once, and enough slowly dissolves to prevent coagulation. At the same time nothing has been added to interfere with measurements of lymph flow and composition.

The removal of the upper two or three ribs and the corresponding section of the sternum exposes the blood vessels leaving the heart and those at the base of the neck, so that it is extremely easy, if the operator wishes to do so, to cannulate the thoracic and right lymphatic ducts in addition to the lung lymphatics.

The lymph in the lung lymphatic cannula is pipetted into weighed tubes, which at precise intervals are set aside and weighed in order to give the volume of flow in milligrams per minute. This measurement made, the lymph is available for cell counts or for chemical analyses. Up to now, time has permitted no more than cell counts with quantitations of total protein by means of the refractometer. Other analyses would be easy, since under steady ventilation and normal blood gas content the lymph flow becomes very constant, and collections may be continued until amounts required for extensive analyses are secured.

The volume of lymph collected usually becomes constant within thirty minutes after collections are started. In eighteen of our dogs it averaged 17.9 mg. per minute, with great variation from animal to animal and in these eighteen experiments without assignable cause. The same variability in lymph flow is found all over the body and has always been a mystery. One generalization can be relied upon. Once lymph flow becomes

steady, whether at low or high volume per minute and wherever collected, it holds the level reached through many hours unless the condition of the animal is altered. The highest flow in the eighteen dogs was 59.4 mg. per minute, and the lowest 3.7, the weight of the first dog being 13.0 kg. and that of the second 11.2. Possibly a period of uniform diet and water intake would give some degree of uniformity per kilogram of weight. The answer does not depend on simple additions of fluid, since all animals received 20 cc. of Ringer's solution per kilogram intravenously at the start of the experiment, in order to insure a good supply of fluid in the tissues. In the same eighteen dogs lymph protein concentrations averaged 3.66 per cent, the highest figure being 4.65 per cent and the lowest 2.81 per cent, with no correlation between these figures and the amount of lymph collected per minute.

The erythrocytes in normal lung lymph varied from a single instance in which none were found to a maximum of 30,700 per cubic millimeter. It was noticeable that the red cells diminished as the speed and competence of the operative procedures improved. The lymph collected had passed through one or more nodes and, as is always the case after such passages, lymphocytes were fairly numerous, averaging 22,206 per cubic millimeter, with a range between 100 and 76,400 in different dogs. This seems a tremendous variation but is found wherever lymph is collected after passing through nodes.

The effects of lung movements are shown in Figure 26. In *A*, the ventilation, during a control period, was 2.5 liters of air per minute. On increasing to 4.3 liters per minute (between the vertical lines 1 and 2), lymph flow decreased and remained at a lower level until the first minute volume of 2.5 liters was restored. Figure 26, *B*, is a series of curves made during an experiment in which rhythmic artificial respiration was replaced (between arrows 1 and 2) by continuous intratracheal insufflation with pure oxygen, the lungs being held motionless in approximately the degree of distention which was maximal during the positive blast of the artificial respiration pump. Again lymph flow was sharply reduced, this time as a result of cessation of motion without abnormal distention. In an experiment such as this with no lung movement, it is probable that pulsation of the pulmonary vessels is the main cause for such lymph flow as occurs.

Of even greater interest are the effects of lowering the blood oxygen, as shown in Figure 27. In this case lymph flow, *L.L.* in the second curve from the top, was about 10 mg. per minute during a control period of almost two hours in which oxygen alone was used in ventilation. Two samples of arterial blood taken during this period contained 19.3 and 20.6 cc. of oxygen per 100 cc. (lowest curve, Fig. 27). Between the two vertical lines, a mixture of 8.6 per cent oxygen and 91.4 per cent nitrogen was substituted

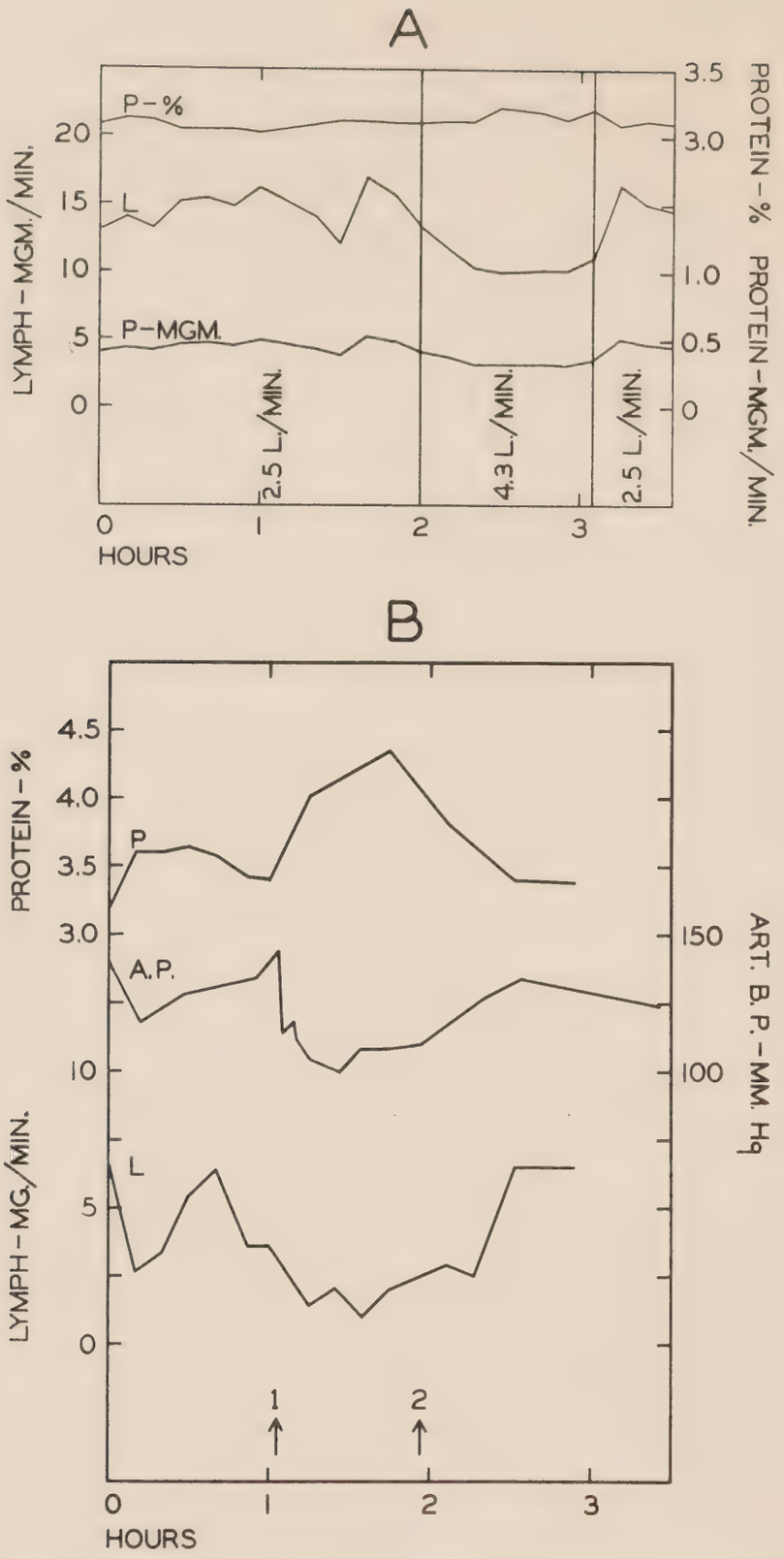


FIG. 26.—Flow and protein content of lung lymph as influenced by changes in lung movement. Between the vertical lines of *A*, rhythmical artificial respiration was increased from 2.5 to 4.3 liters per minute. Between arrows 1 and 2 of *B*, rhythmical artificial respiration was replaced by continuous intratracheal insufflation of oxygen, so adjusted as to maintain the inflation of the lungs less than at the point of previous maximum distention during the positive blast from the respiration pump. *A, upper curve,* lymph protein in per cent; *middle curve,* lymph flow in milligrams per minute; *lower curve,* amount of protein per milligrams of lymph. *B, upper curve,* lymph protein in per cent; *middle curve,* arterial blood pressure in millimeters of mercury; *lower curve,* lymph flow in milligrams per minute. *Ordinates, A* and *B* as designated; *abscissae,* time in hours. (From Warren and Drinker, 1942, Figs. 2 and 3.)

for the 100 per cent oxygen. The change expressed itself rapidly in the arterial oxygen, which fell steadily during the seventy-eight minutes of ventilation with the low oxygen mixture, reaching 4.42 cc. per 100 cc. At

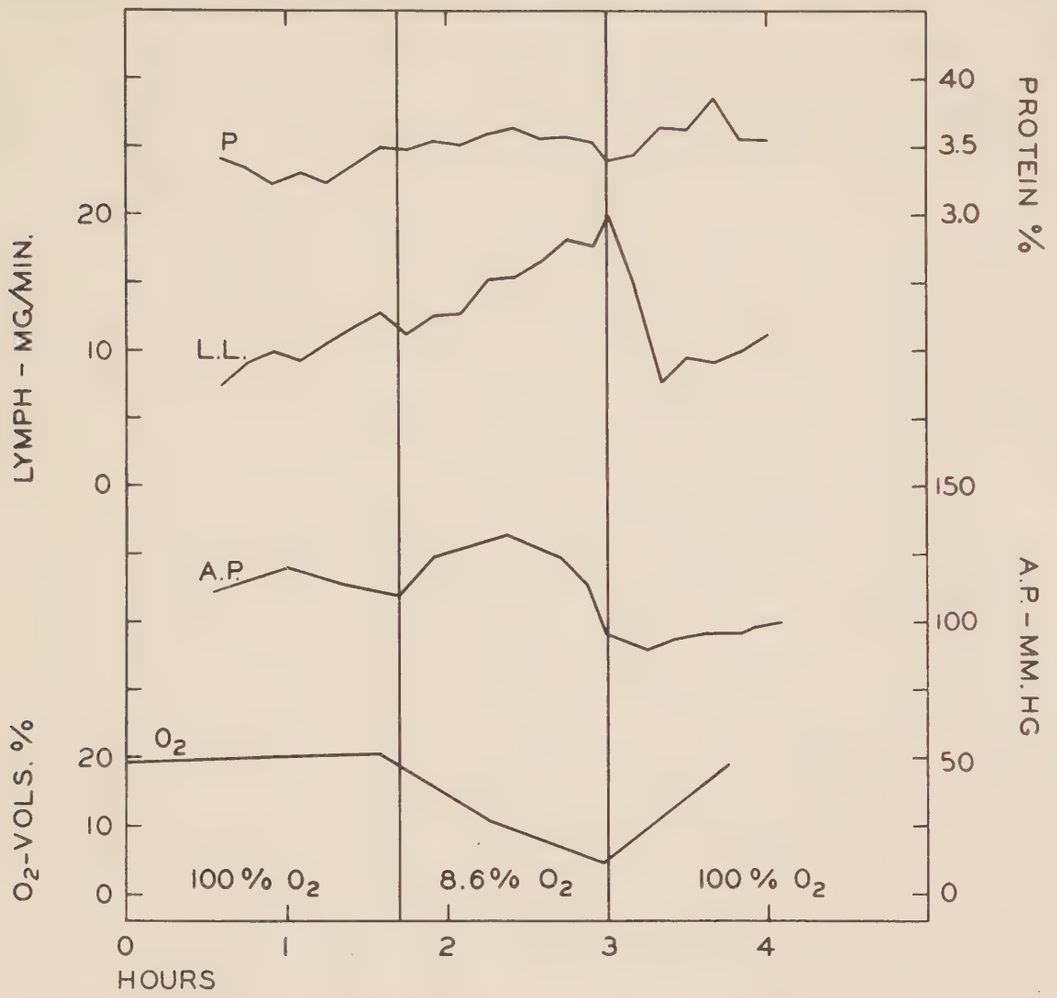


FIG. 27.—The effects of anoxemia upon pulmonary lymph flow and lymph composition. *Top curve,* lymph protein in per cent; *second curve,* lymph flow from the lungs in milligrams per minute; *third curve,* systemic blood pressure; *fourth and lowest curve,* oxygen content of arterial blood in volumes per cent. Between the vertical lines the artificial respiration was shifted from 100 per cent oxygen to a mixture of 8.6 per cent oxygen and 91.4 per cent nitrogen. *Ordinates,* as designated; *abscissae,* time in hours. (From Warren and Drinker, 1942, Fig. 4.)

the second vertical line, 100 per cent oxygen was given once more, and the arterial oxygen at once began to rise.

The effect of this period of anoxemia on lymph flow is marked, as is easily seen in curve 2 (*L.L.,* Fig. 27). The increased lymph production is referable to anoxemia alone, since lung movement—determined by the artificial respiration pump—was constant through the entire experiment, and the arterial pressure (curve 3, *A.P.,* Fig. 27) did not reach a serious level

during the anoxemia, though the fall in progress would have proved dangerous had the anoxemia continued.

The lessons of this experiment, and it has been repeated frequently, are that anoxemia at once increases leakage from the lung capillaries. When this happens, the transudate must first enter the lung tissue, passing into the alveoli after accumulation has progressed beyond the capacity of the tissues to hold the fluid, and beyond the rate at which lymph flow accomplishes removal. This last means of getting rid of extravascular fluid is unimpressive volumetrically. Lymph flow never accounts for any great volume of drainage from any region. It does little to decrease the amount of fluid in edema or in such conditions as attend the removal of fluid from the peritoneal sac in peritonitis. There is, however, reason to believe that the constant outflow of tissue fluid protein by the lymphatic route does diminish the water-holding power of the edema fluid and thus facilitates absorption by the blood capillaries, whenever this becomes possible.

The most interesting and very practical feature of the experiment cited is the fact that a poor supply of oxygen caused increase in lung lymph. This meant abnormal leakage of proteinized fluid into the alveolar walls and eventually into the alveoli. In other experiments, lymph flow rose more abruptly than in the one shown in Figure 27. If ventilation with inadequate oxygen is continued, sooner or later the lymph becomes bloody. These facts mean that when the alveolar capillaries are subjected to oxygen lack their permeability is increased. First there is edema of the alveolar walls, later free fluid in the alveoli. These accumulations in the lung increase the difficulty of oxygen diffusion into the alveolar blood. The same increase in capillary leakage due to low oxygen supply has been demonstrated for vessels in the skin and in the heart. While the resulting edema in such tissues is abnormal, it is not part of a vicious process which, as it continues, makes more and more difficult access of oxygen to the lung capillaries and mounting difficulty in sustaining adequate blood oxygen.

For physicians who are confronted with patients requiring oxygen, it is clear enough that the longer the delay in administering oxygen, the greater the difficulty in getting it into the blood, provided oxygen lack is real and promises to continue. I remember how unhappily the chain of events in the lungs defeated us, when, just as my brother had finished the first workable respirator, an epidemic of poliomyelitis came upon Boston. The appliance was in action at once, and before long two things were apparent: first, that children with failing respiration and unabated or rising fever usually died, in spite of anything the respirator could do. This experience, while bad enough, was an expression of the severity of the particular case and was not so distressing as to find a child fever-free—the acute stage of the disease over—but breathing very ineffectively, cyanotic, and with bubbling râles

throughout the lungs. Placed in the respirator and given oxygen instead of air, such patients sometimes recovered. But often the period of oxygen lack had gone too far and, though the effort to supply oxygen was the best that could be managed, oxygen was to a degree barred from the blood, and death resulted.

The administration of oxygen is of little use when death has reached the door. It must start before the need of it is certain. Many times the use of oxygen results in unnecessary disturbance but, if one waits too long, death will be knocking when the physician tries to turn him away. Oxygen lack, in the end, kills us all, whatever the first cause may be. But—so far as the lungs are concerned—oxygen lack promotes oxygen lack, and while in the early stages the evil cycle is readily broken, after a time the chance of checking what has really progressed is gone, and death, ceasing to knock at the door, is suddenly at the bedside.

The gradual effects of oxygen lack in the lungs are seen clinically in their most uncomplicated form during the slow failure of breathing which occurs in poliomyelitis. The experiment I have described is a fair representation of what goes on during one of the most distressing experiences which can confront a physician. More commonly oxygen lack, as expressed in the lungs, is seen as patients with chronic valvular disease of the heart begin to near the end. In such cases, pulmonary edema is invariable and, particularly in instances of decompensated mitral stenosis, the edema is due, not only to oxygen lack, but also to persistent increase of pressure in the lung capillaries.

Figures 28 and 29 illustrate an experiment which may prove instructive. In a dog anesthetized with nembutal, the sternum and short sections of the ribs are removed to below the fifth rib in order to make a fairly wide exposure of the heart. The lung lymphatic is cannulated, and the pericardium is slit longitudinally. The cut edges of the pericardium are stitched to the margins of the incision, so that the heart is slung in a sort of pericardial hammock, but in a position which in no way affects the entrance of venous blood. Next, starting from the left side, a heavy, greased ligature is passed under the arch of the pulmonary artery and beneath the junction of the superior vena cava with the right auricle. It emerges within the pericardium upon the right side, being passed finally between the azygos major vein and the uppermost of the pulmonary veins. It is then passed back toward the left, under the inferior vena cava and through the pericardium on the left side of the heart. This results in a loop around the pulmonary veins, just as they enter the left auricle. The two free ends of the loop are threaded through holes in the foot of an L-shaped steel rod, and are fastened to a long screw. When this is turned, the loop is tightened around the veins and draws them against the foot of the L. Constriction of the pulmonary veins

results, but the heart is not affected in any other way. The result is the production of a crude sort of mitral stenosis, except that the obstruction to blood flow is at the entrance, not the exit, of the left auricle (Drinker *et al.*, 1922). The pulmonary vein clamp being fastened in place and the femoral artery cannulated, a stilette cannula is thrust through the wall of the pulmonary artery (Swift *et al.*, 1922), and arrangements are completed for recording systemic and pulmonary arterial pressures during obstruction of the pulmonary veins. In order to observe pressure effects alone without complications due to oxygen lack—a situation which would not be met in patients—the lungs are ventilated by pure oxygen.

A typical experiment, in so far as tracings of the two pressures are concerned, is shown in Figure 28. Figure 29 is a summary of the more important findings. During the first three hours, a control period, the flow of lymph from the lungs remained very steady, as did the systemic blood pressure. The percentage of protein in the lymph rose slightly, but such moderate fluctuations are often seen and are not of significance unless accompanied by other changes. Compression of the pulmonary veins lasted ten minutes. When this artificial block was first established, the systemic pressure fell. This decline lasted during the time the pulmonary vascular system was being stuffed with blood. In all such experiments, when filling begins to be complete, more and more blood goes over the dam. With better filling of the left side of the heart, systemic pressure rises and assumes a steady level parallel to the equally constant high level of the pulmonary arterial pressure. When pulmonary vein constriction was released, as seen in the third part of Figure 28, the blood pooled in the lung vessels rushed into the left side of the heart, and a sudden rise in systemic pressure ensued, followed by a gradual return to the original level. At the same time, pressure in the pulmonary artery fell.

Just before opening the pericardium, arterial oxygen was 18.2 cc. per 100 cc. of blood, with 39.2 cc. of carbon dioxide. At the moment of tightening the clamp on the pulmonary veins, the figures were: oxygen, 15.8 cc. and carbon dioxide, 40.1 cc. Eight minutes after clamping was established, oxygen was 14.7 cc. and carbon dioxide, 38.3 cc. Seventy-eight minutes after releasing the clamp, the oxygen had risen to 16.5 cc., with carbon dioxide at 39.7 cc.

In this experiment oxygen lack was not entirely avoided by ventilating with pure oxygen, but did not become abnormally serious, so that the effects upon lymph production were probably ascribable to increased pressure in the pulmonary capillaries. The experiment has been repeated a number of times, and always results in a large increase in lymph flow. The increase may begin before the compression clamp is released, but always rises with extreme rapidity on return to normal conditions. The lymph invariably

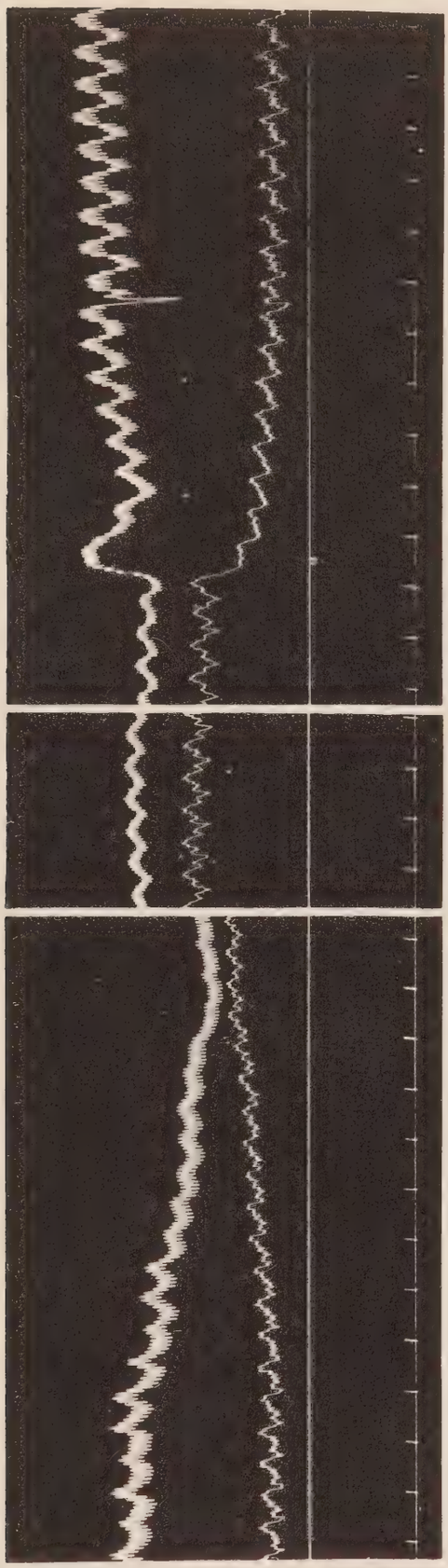


FIG. 28.—Systemic and pulmonary arterial pressures before, during, and after compression of the pulmonary veins at their entrance into the left auricle. *Upper tracing*, pressure in femoral artery; *lower tracing*, pressure in pulmonary artery; *straight line*, path of signal marker and base for mercury manometer recording pulmonary arterial pressure; *bottom line*, time in 6-second intervals and base for mercury manometer recording systemic blood pressure. *1*, tightening of adjustable clamp for compression of pulmonary veins began prior to left edge of tracing. Actual effects, lowering of the systemic and raising of the pulmonary pressure, are evident about 18 seconds from left margin of tracing. *2*, the average height of the two pressures during 10 minutes of pulmonary vein compression. *3*, at the double mark, pressure on the veins was released, with prompt return to original conditions. (From Warren and Drinker, 1942, Fig. 5.)

becomes very bloody. The sequence of events in connection with lymph flow does not mean that leakage from blood capillaries has not been in progress during the entire period of vein compression and increased capillary pressure. But it does mean that the lung becomes somewhat rigid from oversupply of blood, resembling erectile tissue, and that the movement of lymph is not great until a large increase in tissue fluid makes for a rise in

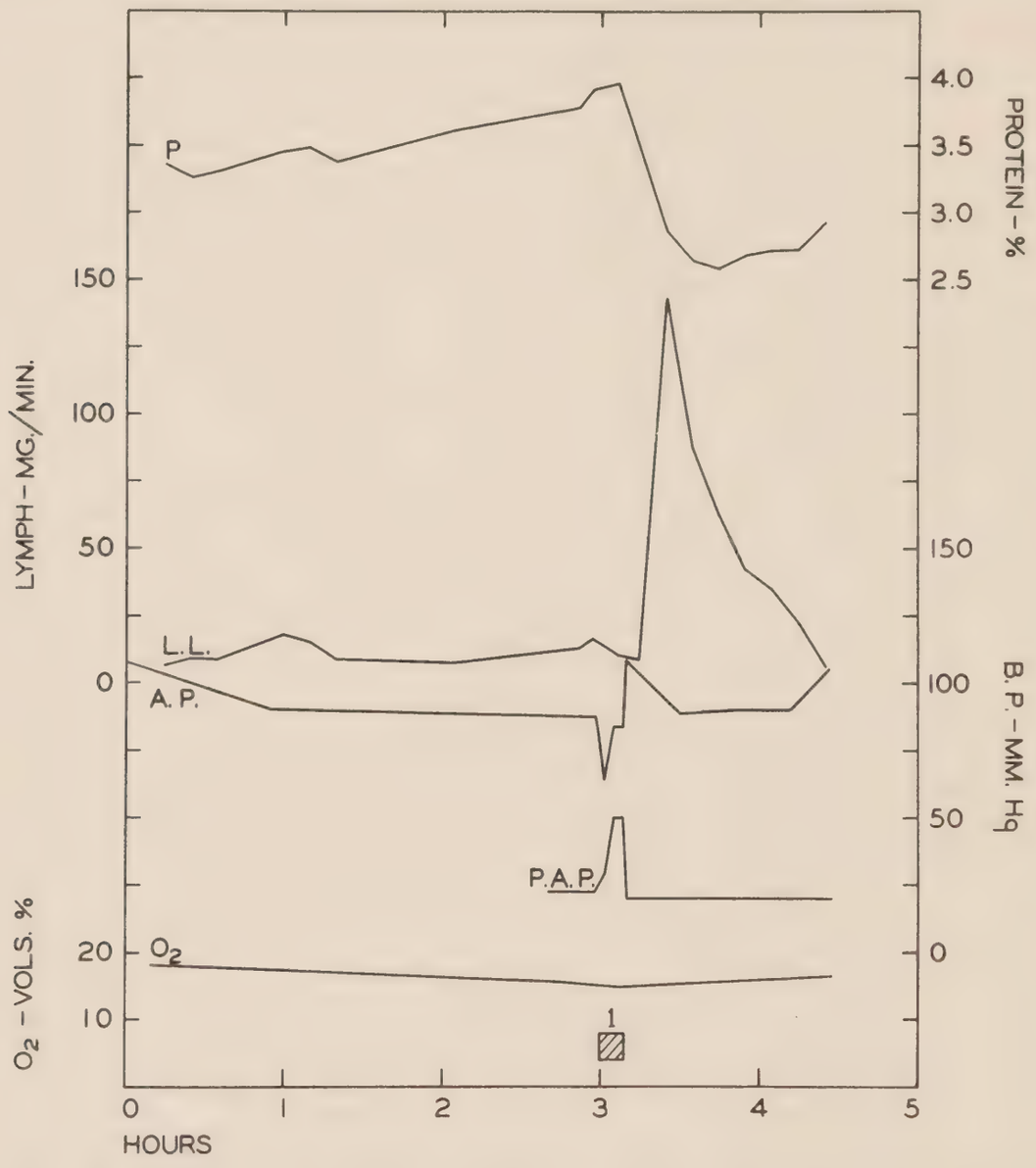


FIG. 29.—Diagrammatic summary of the experiment in which the tracings shown in Figure 28 were made. *Upper curve, P,* protein in lung lymph in per cent; *second curve, L.L.,* flow of lung lymph in milligrams per minute; *third curve, A.P.,* pressure in femoral artery in millimeters of mercury; *fourth curve, P.A.P.,* pressure in pulmonary artery; *fifth curve,* $O_2$, arterial oxygen in cubic centimeters per 100 cc. of blood. Hatched square indicates period of pressure on pulmonary veins. Ordinates and abscissae as designated. (From Warren and Drinker, 1942, Fig. 6.)

lymph flow, or until, as in the experiment I have described, after a relatively short period of blood stasis there is sudden return to normal.

If I summarize what has been learned as to the lung lymph or, better, the relations between blood and lymph in the lungs, it comes to this: The lung capillaries contain blood at low pressures, and their walls are not conspicuously permeable. The vascular system, though great in extent, must receive minute by minute the same amount of blood as the left ventricle delivers to the whole body. The lung capillaries are so placed as to be ready sufferers from oxygen lack. The blood that comes to them has already lost oxygen to the tissues, and they are the first to feel a drop in alveolar oxygen or interference with easy diffusion of oxygen from the alveoli into the blood.

Oxygen lack is a potent cause of capillary leakage and thus promotes edema wherever it occurs, but abnormal amounts of fluid in the lung tissue are peculiarly undesirable. A widespread system of lymphatics is, therefore, not out of place. Furthermore, though increases in capillary pressure due to forceful contractions of the right ventricle are not greatly to be feared, any failure of the left ventricle means increase in pulmonary blood volume, with possible increase in capillary pressure and the prospect of some degree of oxygen lack.

All these factors, which are obvious enough, became realities for me only after direct experiments began to show that the lungs were as much in need of lymphatics as were other parts of the body, and this quite aside from the vulnerability of the lungs to disease. Of this last functional requirement of the lung lymphatics, I shall say a little in the final lecture.

In closing this lecture, I can again leave you with the fact that wherever lymphatics are found and however specialized their situation may seem to be, as in the lungs, these vessels are but allies of the blood capillaries. Their entire task is far from known. But, wherever found, their performance—examined by direct experiment—conforms to a general pattern, which here and there varies slightly, but always in the direction of efficiency, not of principle.

# V. RELATIONS OF THE LYMPHATIC SYSTEM TO PRACTICAL PROBLEMS IN SURGERY AND MEDICINE


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It has been evident in the course of these lectures that considerations of the normal physiology of the lymphatic system require constant reference to the experiments performed by disease. This fact has made much of the preceding material in the nature of applied physiology. To emphasize further the way in which the lymphatic system steadily enters into clinical matters, I would like to finish these lectures by concentrating your attention upon two common conditions, the first surgical, and the second medical. These will perhaps serve to fix the lymphatics even closer to ordinary clinical experience than they may have seemed to stand.

Let us consider first the problem of wound healing. Suppose the skin—which, for the sake of argument, has been made completely sterile—is cut with a thin and extremely sharp, sterile razor blade. Bleeding results; but the bleeding stops, and then the edges of the wound may be brought together tightly and as precisely apposed as before the cut. Healing will take place without swelling, without pain, and without leaving a trace of where the wound was made. So simple an experiment teaches more than one might expect. The cut did not really disturb the normal condition of the skin. Blood escaped from severed capillaries, but this escape ceased, owing to contraction of the vessels or to sterile plugs of fibrin. Inevitably a few red cells and a small amount of serum were imprisoned in the line of the incision when bleeding ceased and the edges of the wound were brought together. The task of getting rid of such slight additions to the extravascular environment is really not abnormal. It is in the regular line of duty of the lymphatics.

If, under local anesthesia, you cannulate an ankle lymphatic in the skin of a dog or in man—we have done so in ourselves—the lymph obtained by gentle massage of the foot or during walking always contains a few erythro-

cytes, and if you massage vigorously they become quite numerous. Hard muscular exercise is even more effective in causing red cell accumulations in such lymph; and if exercise is accompanied by light pressure upon the veins of the thigh, the lymph may become grossly bloody.

These simple facts, expressing the entrance of lymphatic drainage into very ordinary situations, make it easy to see that a few red cells and a little serum scattered in the tissues about a sterile wound will promptly become part of the lymph from the part. Red cells and blood proteins are normal constituents of the lymph even in the absence of a wound, and their removal through the lymphatics is of no moment unless they are present in large amounts. In the first lecture I called attention to a diagram (Fig. 2, p. 16) which summarized the relations between blood, tissue fluid, and lymph, and have repeated—until I am sure you have begun to think of it, not as an important fact in medicine, but as a Harvard obsession—the statement that this arrangement has to do with maintaining the constancy of composition and volume so essential in the tissue fluid.

In medicine and surgery we fail to think of the fact that the only way the tissue fluid can be kept constant is by constant change. Consider a pool full of living things, whose lives depend on what they gain from the inflowing water. They will become ill or die, lacking some arrangement for steady renewal of the supply of water. At the same time, the pool will become a bad sort of place if excess raw materials and waste products are not removed. There is but one road to constancy of tissue fluid composition, and that is steady renewal of water and solutes and equally steady removal of excess and waste. There would be no need for this unending change, if the extravascular pool of tissue fluid were filled with dead, insoluble material; but the body cells, though varying in their needs, all take their share from the tissue fluid, and unless there is provision for supply and removal abnormalities in the fluid are inevitable.

Little has been said about absorption of water and simple salts by the blood capillaries, a phase of the general problem which has been far more widely studied than has the function of the lymph capillaries. Absorption into the blood is the great means for quick adjustment of the volume of the tissue fluid. Fifty cubic centimeters of physiological salt solution, injected subcutaneously, disappear almost at once, and the quieter the part, the quicker goes the fluid—that is, the lower the capillary blood pressure, the greater the effective colloid osmotic pressure of the plasma proteins and the more rapid the reduction of swelling. In contrast, inject 25 cc. of sterile serum taken from your own blood. An indurated, painful area results, and the quieter the part the longer the annoyance persists.

How do these simple matters relate to wounds and especially to the part played by the lymphatics in wound healing? First of all, swelling means a

certain degree of tissue fluid stagnation. It is true that the water in a large pond may be changed as steadily and as rapidly as in a small one, but this analogy does not apply to the situation. When inflammation and swelling occur, the supplying system, the blood capillaries, though guarded against extremities of leakage, does release more water and solutes than under normal circumstances. The mechanism for supply becomes larger and the walls of the capillaries more permeable. The lymphatics, on the other hand, though not compressed in swollen tissue, are not changed to accomplish an increased measure of absorption and removal of inflammatory exudates. Furthermore, if the inflamed part is held quiet and swelling is not excessive, lymph flow increases but little, since in quiescence it depends on the feeble impact from pulsation of near-by blood vessels and eventually upon augmented tissue pressure; but this last is not effective until swelling and tenseness are advanced, and is seen at its best when swelling occurs rapidly.

If the foot of an anesthetized dog is dipped in water hot enough to cause a burn but no breach in the tissues, the part swells rapidly, and lymph which is practically blood plasma may pour from the draining lymphatic. Eventually the pressure in the tissues may become that of the arterioles and as a result lymph moves rapidly out of the part.

An injury of this sort, with no infection and no break in tissue continuity, is not the same as the usual type of infected wound, though in the end many of the things that occur are quite similar. Suppose a dirt-filled wound is encountered, with a considerable break in the tissues and the establishment of fairly persistent inflammation. Around the edges of the wound and for some distance into the tissue, swelling will be evident, with all of the other classical signs of inflammation. If the wound drains externally, fluid—practically blood plasma—leaking freely from overdilated capillaries, escapes readily; but there is always a slight excess of highly proteinized tissue fluid imprisoned in the tissues around the wound, and this exudate, unless utilized *in situ,* finds its way into lymph capillaries and to the nearest lymph nodes. The wound being infected, red streaks extend from the lesion toward the nearest lymph nodes, which swell and become painful. This series of events is common experience. If matters go reasonably well, healing occurs slowly, leaving a scar behind, sometimes a very disfiguring scar.

Let us go further into what really may have been happening. The wound was accompanied by mechanical destruction of tissue, and by implantation of bacteria possessing the capacity to sustain irritation. The blood supply of the region was increased, due to an axone reflex mediated through sensory nerves and resulting in dilatation of arterioles, capillaries, and arteriovenous anastomoses. Swelling occurred, not kept down by leakage of fluid exudate from the wound surfaces; and, owing to dilated capillaries, highly proteinized tissue fluid, cellular detritus, and bacteria collected

in the tissue bordering the lesion. With this local increase in tissue fluid, plus a variable degree of cellular mutilation, clotting occurred, and this increased the extravascular stagnation of fluid. The degree of clotting is never predictable nor is the extent to which clots fill capillary lymphatics and block entrance into them. In any event, the region has become one of localized lymphedema, an area where the tissues are bathed in a highly proteinized fluid containing fragments of wounded cells. At the same time, capillary blood flow has continued and the supply of oxygen, etc., been held reasonably normal. Very soon fibroblasts begin to proliferate, and in time the open wound becomes an ugly red scar with no swelling about it.

The rapid re-establishment of lymph drainage after complete lymphatic section has been described. It is an extremely fundamental matter, and about an infected wound lymphatics soon begin to carry off excess blood protein, bacteria, red cells, and even particles of dirt. It has been held that fibrin plugs in blood capillaries and lymphatics isolate such lesions and protect the body from general infection. In my opinion, based upon collection of lymph from foci of infection, this protection through isolation is very imperfect. Fibrin formed in lymphatics contracts after a short time; and if draining vessels from the lesion are cannulated, they soon display a free flow of lymph, which increases markedly as the tissue swells and tissue pressure begins to resemble arteriolar pressure.

The whole train of events sums up very simply. An area of tissue has been flooded by a concentrated filtrate from the blood. This excess of tissue fluid—plus cellular detritus, etc., which may be poured out over a considerable period, depending upon the presence of a bacterial irritant capable of causing persistent vascular dilatation—may escape from the surface of the wound; but some of it lies stagnant in the bordering tissues, draining off slowly through the lymphatics, which—owing to quiescence of the part and fibrin formation—do not carry off what must be removed in order to restore the tissue fluid to normal composition and volume.

The isolation of inflammatory processes, particularly those due to infection, is apparently desirable. But carry the whole analysis a little farther. If you block lymphatics to a part—the leg of a dog, for example—lymphedema occurs and elephantiasis follows. Studies of the edema fluid reveal high concentration of blood proteins, 2.5 to 4.0 per cent; if inflammation is present, the figure may rise to 5.5 per cent. This sequence of events is often seen here in the Temperate Zone in patients with lymphedema, and is extremely frequent in tropical regions where filarial infection is common.

In my opinion, the same series of facts applies in the case of the wound under discussion. There is rapid production of tissue fluid from the overdilated vessels in the inflamed tissue. This fluid is highly proteinized, and always contains cellular detritus. It is removed slowly, due to the forma-

tion of fibrin in the injured region and even more to the fact that the parts subjected to such lesions are held as motionless as possible. Entrance of tissue fluid into lymph capillaries, consequently, and movement along valved trunks are sluggish compared to the rate of accumulation in the tissue. Sometimes, when the infecting organism is dangerous, the host benefits by localization of the process at the original site, and not infrequently external drainage is of material assistance in keeping infection out of the lymphatic system.

But, with concentration and stagnation of tissue fluid, there goes inevitably the possibility of increased fibrous overgrowth and heavy scarring. A bad scar is, then, an expression not only of the necessity to fill in a cavity in the tissues but also of fibroblastic overgrowth—such as is seen diffusely when the lymph drainage of a part is blocked, and particularly when inflammation, with accompanying increase in capillary leakage, intensifies the accumulation of substances which should be removed by the lymphatics.

Like many of the reactions of the body to disease, the healing of infected wounds is a mixture of good and bad processes, and intelligent treatment depends upon measures which promote the first and restrain the second. I have said that when lymph drainage is blocked fibrous growth occurs, and may continue for years. I have spoken of the work of Whipple and his collaborators indicating that dogs could be kept in nitrogenous equilibrium by intravenous injections of dog serum, which were their single source of protein. It is the fact that normal dog plasma given intravenously to protein-starved dogs keeps them in health for weeks at a time (Madden and Whipple, 1940; Madden *et al.,* 1941). This means that somehow or other protein reaching the body through the blood may be utilized. The problem as to how this is brought about is still unsolved, and I shall not risk the reputation of these lectures by guessing at the answer. Before many years have passed, experiments will provide the solution. It will be profitable, however, to list certain things which are well established, and which bear upon a line of advance certain to be important for the treatment of disease. These facts are as follows:

1. Blood capillaries practically all over the body leak a small amount of plasma protein into the tissue fluid, as evidenced by the constant finding of serum albumin, globulin, and fibrinogen in lymph, which has now been collected from many different organs and tissues.

2. Plasma protein can be used as a source of all protein.

3. Plasma protein is apparently a store of circulating material, normally used to some degree by the tissues, but capable of wide usage under conditions of need.

4. There is no decisive evidence as to whether tissue cells take up the extravascular protein as such, break it down, and resynthesize the particu-

lar protein they require, or whether a small concentration of a proteolytic enzyme in the tissue fluid causes a minimal amount of digestion, and the cells absorb what they need.

5. Under ordinary circumstances, the normal activity of the mammal maintains a constant circulation of plasma protein from the blood capillaries, through the tissue fluid, into the lymphatics and back to the blood. Stagnation and accumulation of tissue fluid are abnormal conditions.

6. When capillaries are abnormally permeable, as in inflammation, the inflamed tissue receives an excessive amount of plasma protein, and lymph drainage is not capable of preventing stagnation of this abnormal tissue fluid.

7. Blockage of lymphatics without inflammation slowly results in much the same situation, though, lacking concomitant inflammation, the protein in the fluid from the lymphedematous part never rises to the level of plasma protein concentration, there being a difference of 2 to 4 per cent.

8. Blood supply, blood oxygen, all the common contributions from the capillary blood to a region where lymphatics are obstructed, are normal. In an inflamed area, except in tissue which is necrotic and to which the capillaries are blocked by thrombi, there is also a free supply of oxygen, etc., from the capillaries.

These eight facts seem to me to bear upon wound healing under the general circumstances we have postulated. There are of course other elements in the problem, but through these alone you may reduce many common experiences to rationality and to a predictable outcome. First, the conclusion is unavoidable that in wounded regions, with normal or increased blood supply and excess leakage of plasma protein into the tissue fluid, there will be an oversupply of raw material essential for growing tissue cells. The situation in the tissue fluid is not a novel one, but simply an intensification of the normal state of affairs. During inflammation or when lymphatics are blocked, the regions involved are better provided with materials for cell development, and it is not surprising to encounter proliferation of fibroblasts, which is invariably prominent when tissue growth occurs.

You recollect the astonishing regenerative powers of the lymphatics. Even when there has been severe destruction of tissue, lymphatics will soon be re-established in injured regions, and their walls are permeable to all the substances that may be found in the fluid accumulating in the wounded tissues. But entrance into lymphatics and flow through them depend essentially upon movement, massage, etc., all obviously to be avoided, especially if infection is present. Some degree of edema and swelling are thus inevitable, unless measures are used to prevent them.

It is my belief—and but a suggestion for you—that the extent of fibrous tissue growth, either in the healing of wounds or in elephantiasis, is an expression of the degree of tissue fluid stagnation in regions where there is

adequate flow and oxygenation of capillary blood. The necessity to fill space when tissue has been destroyed adds to the extent of scarring but, even without loss of tissue, unsightly scars may have their cause in prolonged stagnation of concentrated tissue fluid in injured areas.

In medicine and surgery there is always another side to the development of such a general idea as this one relative to wound healing. Sometimes the second argument—or, better, a further group of experiments or clinical studies—makes the first idea ridiculous, and sometimes you are fortunate enough to gain support, where it may not have been expected. Clark (1919) and Harvey and Howes (1930) found that wounds healed slowly when plasma protein was low. Thompson and his associates (1938) reported that wound disruption was more frequent in the presence of hypoproteinemia. In other conditions, such as vitamin C deficiency (Lund and Crandon, 1941) and dehydration, slow healing has also been reported. The vitamin C lack is distinctive, but dehydration, especially if marked, means reduction of free tissue fluid and functionally ought to act as does low protein in the blood. In many operations on elephantiatic parts in dogs, healing is prompt and solid; nor have I heard complaints from my surgical friends as to healing after they have removed several pounds of elephantiatic tissue.

Such observations fall into line with what has been presented relative to tissue fluid composition and proliferation of fibroblasts, and lead toward a certain degree of logic in treating infected wounds. Clearly, release of fluid and solutes from the blood are necessary, but any considerable degree of swelling and stagnation of tissue fluid are undesirable. The increased permeability of the blood capillaries provides automatically for free delivery of fluid from the blood to the tissues, but with this increase in supply there is little accompanying provision for removal. The part is immobilized, either artificially or because of pain; and lymph movement depends, not upon the usual influences, but upon the gradual increase in tissue pressure, aided to an insignificant extent by pulsation of the blood vessels. Very soon the rate of change of tissue fluid is greatly reduced, and the cells find themselves in a pool of highly proteinized fluid containing cellular detritus, micro-organisms, etc. It is bad policy to promote lymph flow in order to readjust the situation toward normal. Absolute quiet, often with the part raised so as to reduce venous pressure, is used. These measures reduce capillary blood pressure and production of exudate. There is greater comfort at once, as increasing tension is checked. At the same time, there has been little cause for increased lymph flow. It is a New Deal sort of therapy, control of production and nothing else.

In addition to quiet and to elevation, external pressure is the final useful physiological measure. This results in a smaller pool of tissue fluid and

more rapid renewal, since pressure which does not reduce the normal volume of the part does not close lymphatics but does reduce the space which can be occupied by fluid leaking from the abnormally permeable capillaries. It also augments lymph movement and absorption of water by the blood capillaries.

The use of such simple treatment must vary with each case. End pressure developed in lymphatics from a seriously inflamed part may reach mean arterial pressure. This must also be the tissue pressure, and is as high as one could expect to find in an area of acute inflammation with rapid swelling. External pressure great enough to restrain such violent bursts of swelling would check capillary blood flow, and would thus be harmful. Pressure is most useful in old lesions with chronically dilated and leaky capillaries, where the tissues are filled with stagnant fluid, which has little means of escape save by slow oozing from the surface. Such areas become thickened, first with edema fluid, later by fibroblastic proliferation. Persistent pressure upon lesions of the nature of chronic leg ulcers prevents accumulation of excess fluid in the tissues, both by reducing filtration from the capillaries and by preventing puddling of excess deoxygenated blood in dilated venules. It is a means of compelling some measure of the normal constant renewal of the tissue fluid.

In the case of new wounds—let us say a compound fracture, such as has been encountered so often as a result of bombing raids—there is a growing interest in providing complete immobilization by means of plaster applied so that swelling is prevented. External drainage is provided by gauze beneath the plaster casing, which allows little swelling but some escape of fluid. The physiological reasoning behind such procedure is, I think, quite sound; but the heritage of wide open drainage areas is pre-Listerian and the Orr-Trueta method loses its value if half done—that is, if the part is immobilized but with a large enough opening in the casing to permit local swelling and stagnation of exudate.

The aim of the surgeon is to manage the injury in such a way as to keep the environment of the tissue cells as normal as possible. To this end, there must first be patient, gentle, and very thorough removal of foreign material and of tissue which has lost its blood supply or is so poorly vascularized as to become necrotic after a time. Every bit of foreign matter or dead tissue will result in exudate from the blood vessels beyond that normal to the tissues. Sterile tissue should rest against sterile tissue when the wound is closed and covered with gauze re-enforced by plaster.

Returning to the patient, with his injury now enclosed in plaster, what can be given as reasons for favorable progress? In the first place, at least in favorable instances, the injured part was confined before inflammatory edema began. Blood supply was normal, and if lymphatics were destroyed

they were soon restored. Curiously enough such patients do not have severe pain, provided inflammatory swelling is not in progress when the plaster is applied; and, as might be expected, lymph drainage is very slight in a quiescent part where edema is restrained (Barnes and Trueta, 1941). Fever does occur and may be persistent for some time; but, if the part below the cast does not swell alarmingly and if lymph nodes do not become badly swollen and painful, the original cast should not be touched but should remain unopened for two or three weeks, in spite of the fact that it may begin, not to smell, but to stink.

The first dressing after removal of the original cast merely means putting on another; and so, in time, these people recover, and they do so more rapidly and with less scarring than if treated by the old open technique with irrigations of varied sorts. Nothing in medicine or surgery works every time, and this procedure requires the salt of common sense, just as do other measures in our art. It depends for success on reducing the lesion to the simple state described, first of all, for the cut by the thin razor blade. The whole procedure is an attempt to make the environment of the body cells as nearly normal as possible. Edema and stagnation of tissue fluid are restrained. There is a steady but slight renewal of the tissue fluid; but the increase in lymph flow seen in swollen parts, particularly if not immobilized, is not encountered; and the spread of infection, with establishment of secondary foci and the eventual involvement of much of the body, is checked. Gas bacillus infection and tetanus are as readily prevented under plaster as with the old open conditions.

There is a final point not to be forgotten. If extensive loss of blood has attended the injury, a transfusion may be necessary; but in this connection it should be remembered that the absolutely quiet patient has many more red cells than he requires. Unless really badly reduced, there is no need for giving them—that is, no need for an ordinary transfusion. Blood protein concentration falls after severe hemorrhage, when water is taken into the blood, and dilute plasma leaks readily from the capillaries, so that edema and swelling are harder to restrain. The practice of giving blood plasma intravenously and, I hope quite soon, concentrates of the blood proteins is much to the point. Such treatment restores the normal colloid osmotic pressure of the blood and balances the increase in capillary pressure which may be present in inflamed tissue. Stagnation of tissue fluid is thus restrained and better conditions for recovery are provided.

To this brief analysis of wound healing, another practical example of the role of the lymphatics may be added, this time drawn from medicine. The persistent inhalation of dust—let us say relatively pure carbonaceous dust from powdered coal—results, after a long time, in diffuse fibrosis of the lungs. Here and there nodular foci are seen; but the essential feature

of the process is the gradual laying down of fibrous tissue, which eventually may interfere seriously with breathing, so that the patient is badly handicapped for anything save the quietest sort of life, and withstands pulmonary infection very badly.

It is agreed that foreign particles, such as those of the coal dust involved in our hypothetical case, either after phagocytosis or independently of it, find their way into the depths of the lung via the lymphatics, and move slowly toward the lymph nodes at the root of the lung, where they come to rest. The dust-filled nodes then undergo a slow process of fibrosis, which in the end may reduce them to black, stony masses far different from their normal appearance. The movement of lymph through such glands, even when they seem extremely abnormal, undoubtedly occurs to some extent, but without doubt some degree of lymphatic obstruction is present. In addition to the black accumulations of carbon in the nodes, the large lymphatics—which run with the arteries, veins, and bronchioles—are seen to be more or less filled with masses of carbon, and are surrounded by thickened strands of fibrous tissue. Within the substance of the lungs, lymph nodes are not found; but accumulations of lymphocytes become more and more numerous as dust deposition increases. The sequence of events is that which always attends lymphatic obstruction, the growth of fibrous tissue, which sooner or later embarrasses normal function.

If, instead of carbon particles, crystalline silica is inhaled, one merely encounters, I believe, a much intensified sort of interference with lymph flow from the lungs. Crystalline silica has a curious and poorly understood ability to induce fibrosis. Particles reaching the lung lymphatics—either within phagocytes or taken up by phagocytes in their passage to the lymph nodes—apparently not only kill the cells which have ingested them, but convert the phagocytes into embalmed foreign bodies, which persist and pile up in masses along the lymph channels. Fibroblastic growth in and around such accumulations of dead cells and silica particles is very intense; and in silicosis one sees first a spattering of the lung tissue with nodular masses, which may progress rapidly into generalized fibrosis, with disastrous encroachment upon the alveoli. Again, I believe that the essential underlying cause is lymphatic blockage.

Normally, as described in the last lecture, lymph moves steadily through the lung lymphatics and back to the blood. If the lymphatics in the leg of a dog are obstructed by repeated intralymphatic injections of crystalline silica, elephantiasis occurs, and there is no logical reason to feel that the lungs are immune from the same process or that silicosis is not in reality a sort of pulmonary elephantiasis. I have sections of the lungs of a man who died after three months' work in an atmosphere heavily charged with particles of crystalline silica, particles so small as to drift like smoke in the

air. These minute particles, if they penetrate the alveolar walls, have but one route ahead of them, the lymphatics, which they are peculiarly adapted to obstruct. While accumulations of fibroblasts will occur in and around masses of dead phagocytes containing particles of silica, the generalized spreading type of fibrosis characteristic of advanced silicosis is also so characteristic of that occurring when lymphatic blockage causes stagnation of tissue fluid that, again, in this common medical condition, I believe one sees further instance of the necessity for free lymph movement if normal conditions are to be maintained.

I am quite aware that in connection with the healing of wounds and in inflammatory exudates there is a certain amount of work which purports to show that specific substances promoting growth are present, particularly in areas of inflammation. This may be the case, and similar substances may be present in the edema fluid from regions where lymphatics have been blocked. It is possible that such substances provide the true explanation for the phenomena of fibrous growth I have described. In my opinion, however, it is more probable that a simpler and more normal process is responsible, one more in accord with normal processes of cell nutrition, and this probability I have endeavored to portray for you.

These practical illustrations, the healing of wounds and the development of lung fibrosis, may seem far more definite than much I have said in earlier lectures. As a matter of fact, the things I have said about them are only ideas—ideas which lack the definiteness of experimental proof with which I have been able to fortify the straightforward anatomy and physiology of other lectures. But ideas do harm in our art only when they are permitted to stand as ideas! Converted through experiment into fact, they are the kindling of our medical knowledge. Medicine tempts us all to thinking, but too often, like the Bandar Log,

> "we sit in a branchy row,
> Thinking of beautiful things we know;
> Dreaming of deeds that we mean to do,
> All complete in a minute or two—
> Something noble and grand and good,
> Won by merely wishing we could."

I have no use for thoughts and ideas, such as those described in this lecture, until experiment turns them into fact; and my only excuse for such an account of ideas is a compelling desire to initiate experiments to answer the questions I have suggested. You will agree that the mysteries of the lymphatic system fall in well with such a compulsion, and if some of you have been infected by its problems, I shall have left you as the founder of this series would have wished.

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